Mind and Heart: the Role of Stress

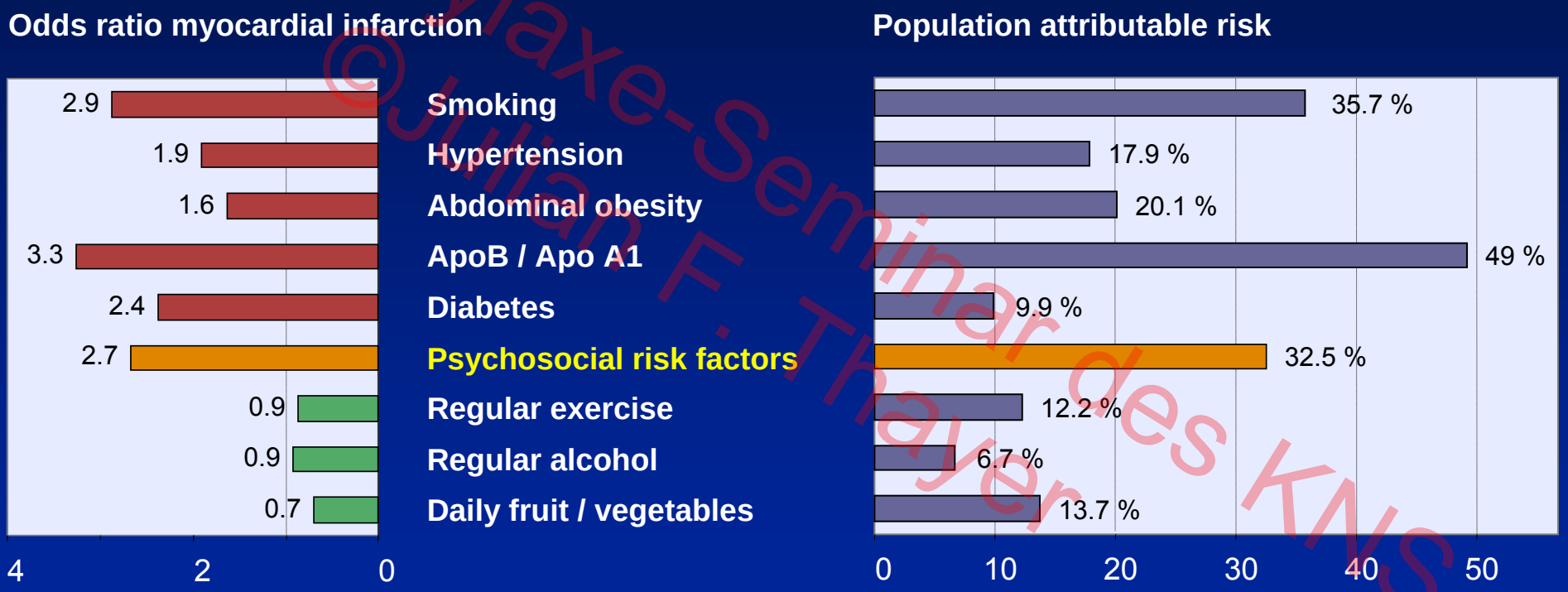
Julian F. Thayer, PhD
The Ohio State University

"Claude Bernard also repeatedly insists, and this deserves especial notice, that when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric (vagus) nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body"

(Darwin, 1872)

Interheart Study (2004)

Case Control Study 52 Countries
15152 Patients with Myocardinfarct
14820 Controls



Lancet 2004, 364:937-52

Anxiety Predicts Mortality and Morbidity After Coronary Artery and Valve Surgery—A 4-Year Follow-Up Study

Andrea Székely, MD, PhD, DEAA, Piroska Balog, PhD, Erzsébet Benkö, MD, Tamás Breuer, MD, Judit Székely, MD, Miklós D. Kertai, MD, PhD, Ferenc Horkay, MD, PhD, Mária S. Kopp, MD, PhD, and Julian F. Thayer, PhD

Psychosomatic Medicine 69:625–631 (2007)

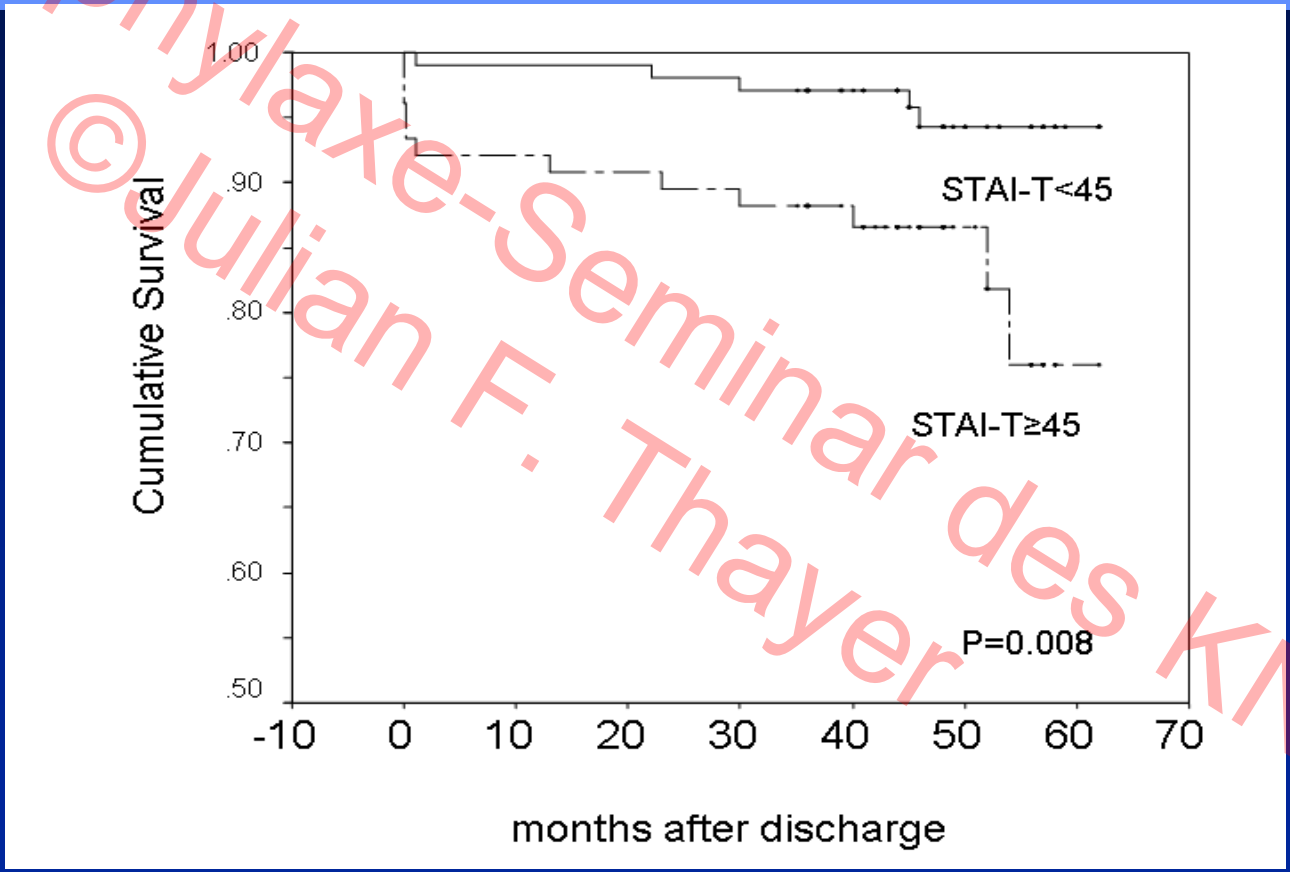
Methods

- In total, 180 patients who underwent cardiac surgery using cardiopulmonary bypass were prospectively studied and followed up for 4 years.
- Anxiety (Spielberger State-Trait Anxiety Inventory, STAI-S/STAI-T), depression (Beck Depression Inventory, BDI), living alone and education level along with clinical risk factors and perioperative characteristics were assessed.
- Psychological self-report questionnaires were completed preoperatively and 6, 12, 24, 36 and 48 months after discharge.
- Clinical end-points were mortality and cardiac events requiring hospitalization during follow-up.

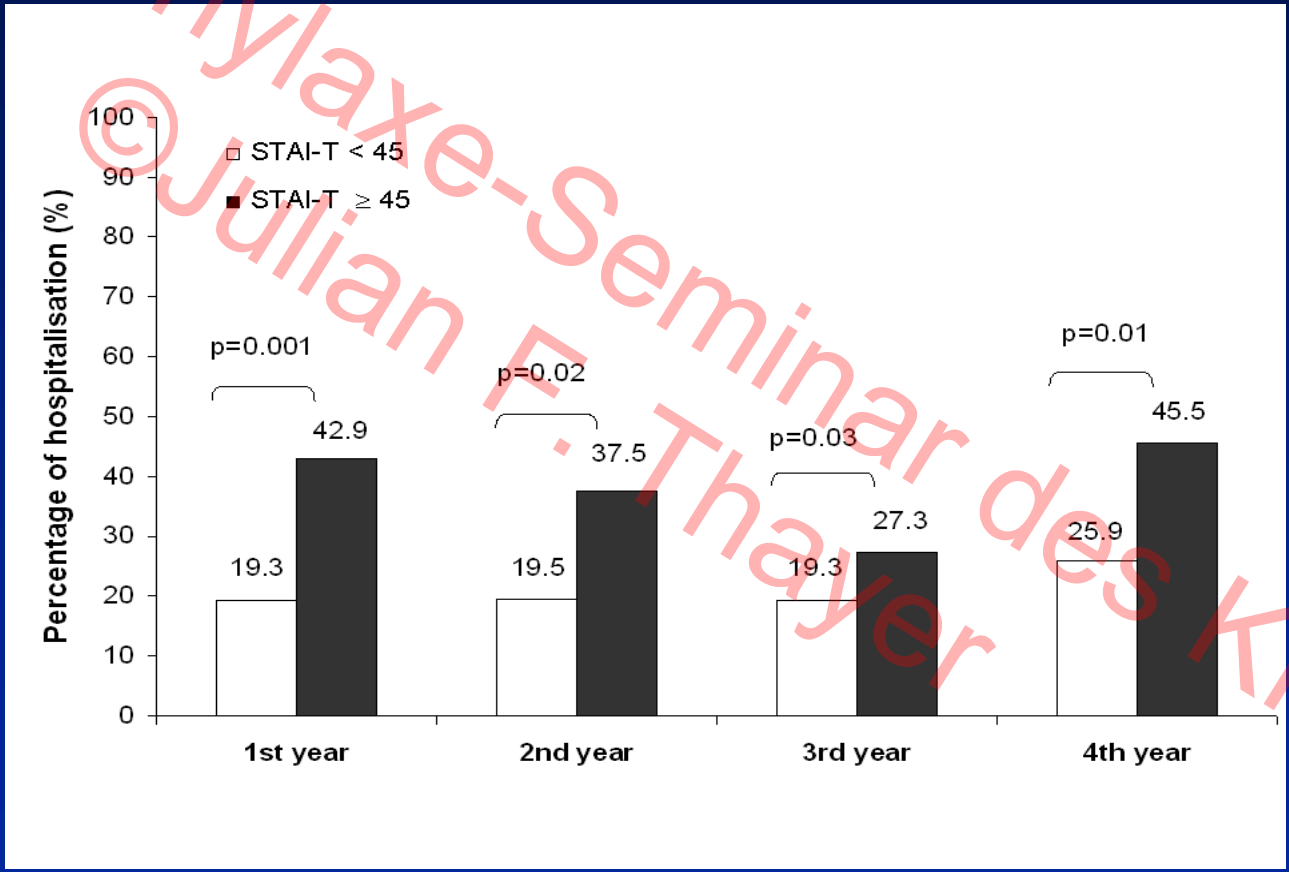
Results

- Kaplan-Meier analysis showed a significant effect of preoperative STAI-T above 45 points (p= 0.008) on mortality.
- In multivariate models postoperative congestive heart failure (OR: 10.8; 95 % confidence interval [CI]:2.9-40.1, p=0.009) and preoperative STAI-T (score OR: 1.07; 95 %CI: 1.01-1.15, p=0.05) were independently associated with mortality.
- The occurrence of cardiovascular hospitalization was independently associated with postoperative Intensive care unit days (OR: 1.41; 95 %CI: 1.01-1.96, p=0.045) and post-discharge 6th month STAI-T (OR: 1.06; 95 %CI:1.01-1.13, p=0.03).

5 Year Survival Curve after CABG



Hospitalizations after CABG surgery



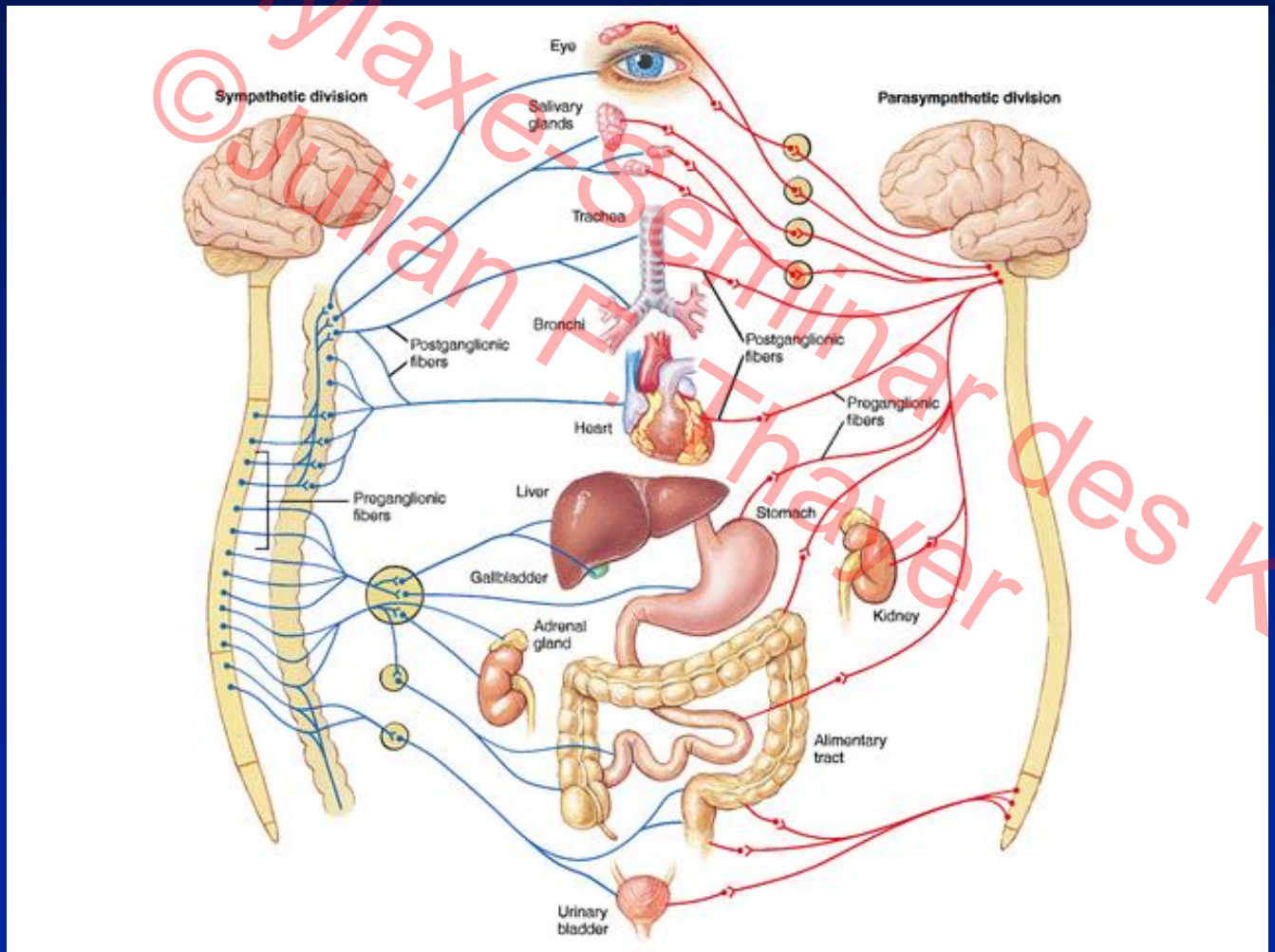
Risk factors for heart disease

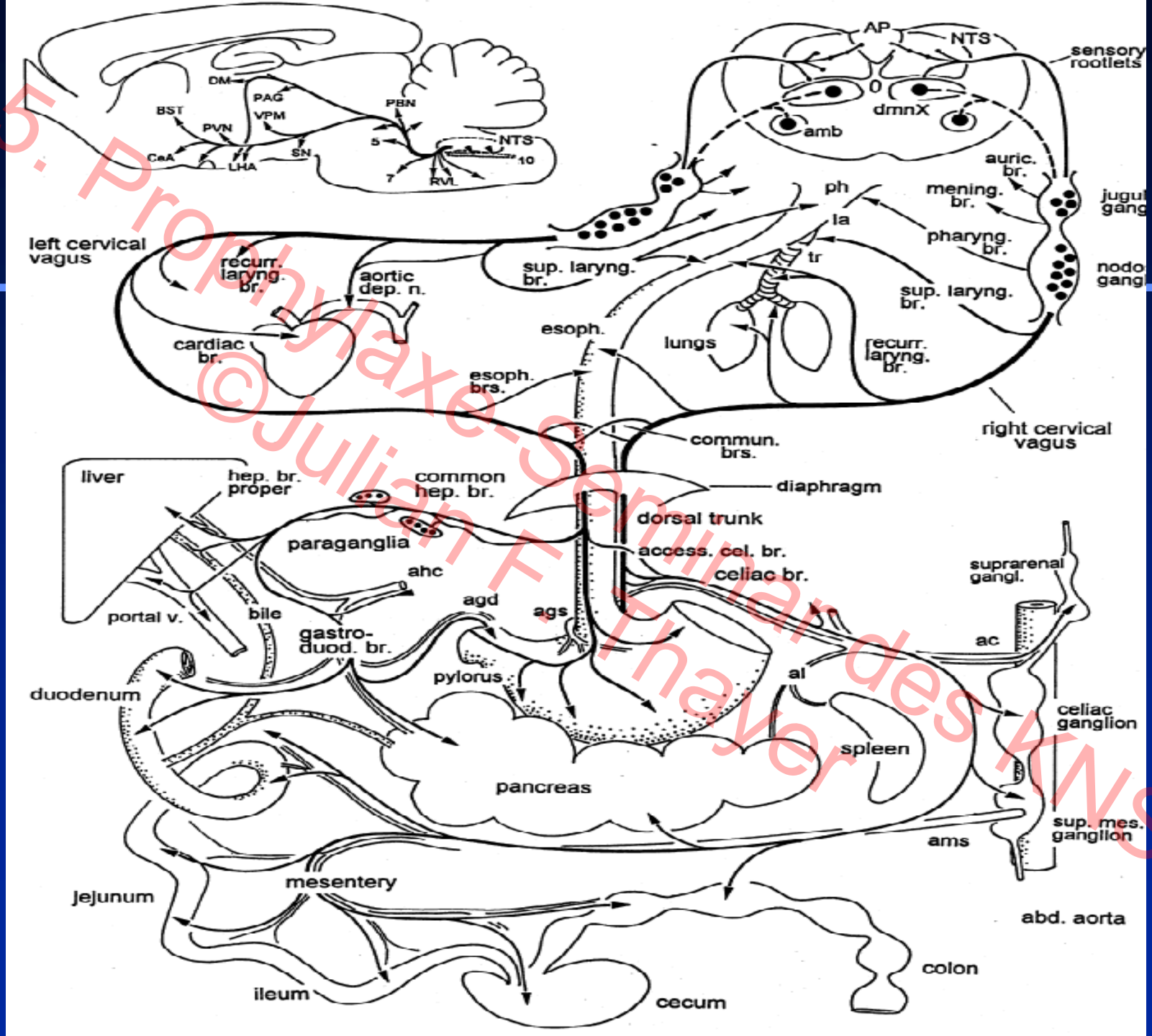
- The NHLBI of the US NIH list 8 risk factors for heart disease and stroke
- Hypertension, diabetes, cholesterol, smoking, obesity, physical inactivity, family history, and age
- Emerging risk factors include inflammation and psycho-social stress
- Each of these risk factors is associated with decreased vagal activity (Thayer & Lane, Biological Psychology, 2007; Thayer et al, Int. J. Card., 2010)

Autonomic Balance

- Predictor of Mortality and Morbidity
- Underlies a broad range of responses linked to allostatic load
- Associated with central nervous system
- may explain how psychosocial factors are instantiated in physiology and disease
- may explain known health disparities

Overview of the autonomic nervous system





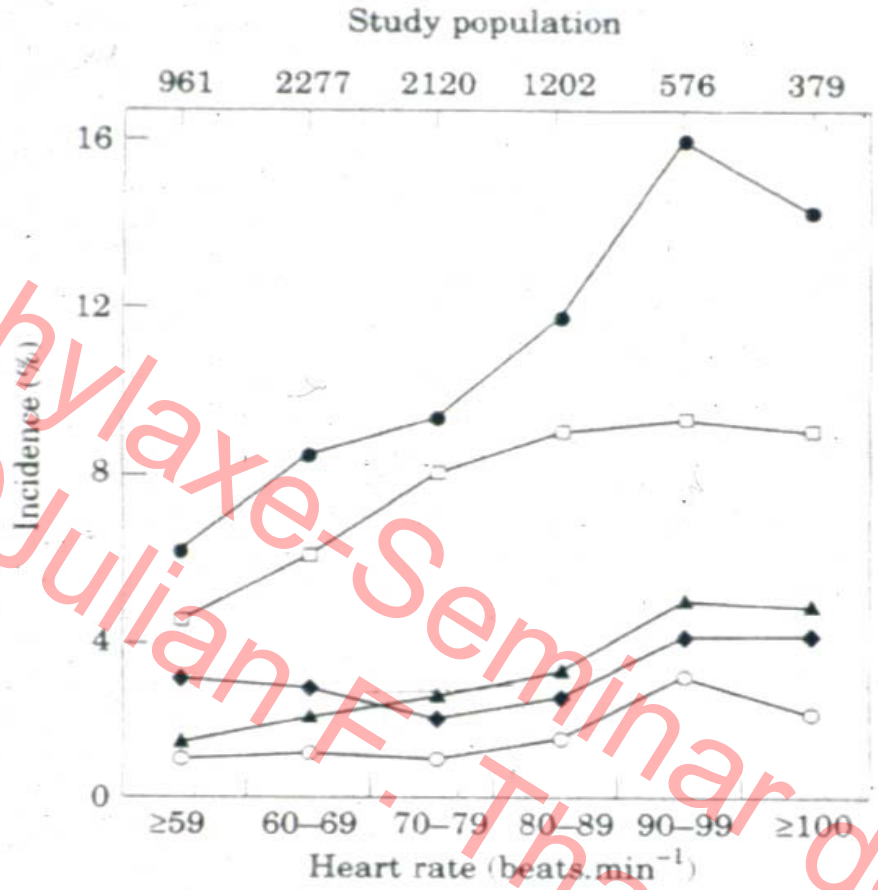


Figure 1 All-cause and cause-specific mortality and heart rate in the general population. ● = total mortality, □ = coronary heart disease, ◆ = other deaths, ▲ = cancer, ○ = stroke. All-cause mortality is 2–3-fold higher in subjects with heart rates higher than 90 beats . min^{-1} compared to those with heart rates <60 beats . min^{-1}. Similarly, coronary heart disease mortality is about twice as high in subjects with heart rates >90 beats . min^{-1} compared with subjects with heart rates <60 beats . min^{-1}. (Adapted with permission[3].)

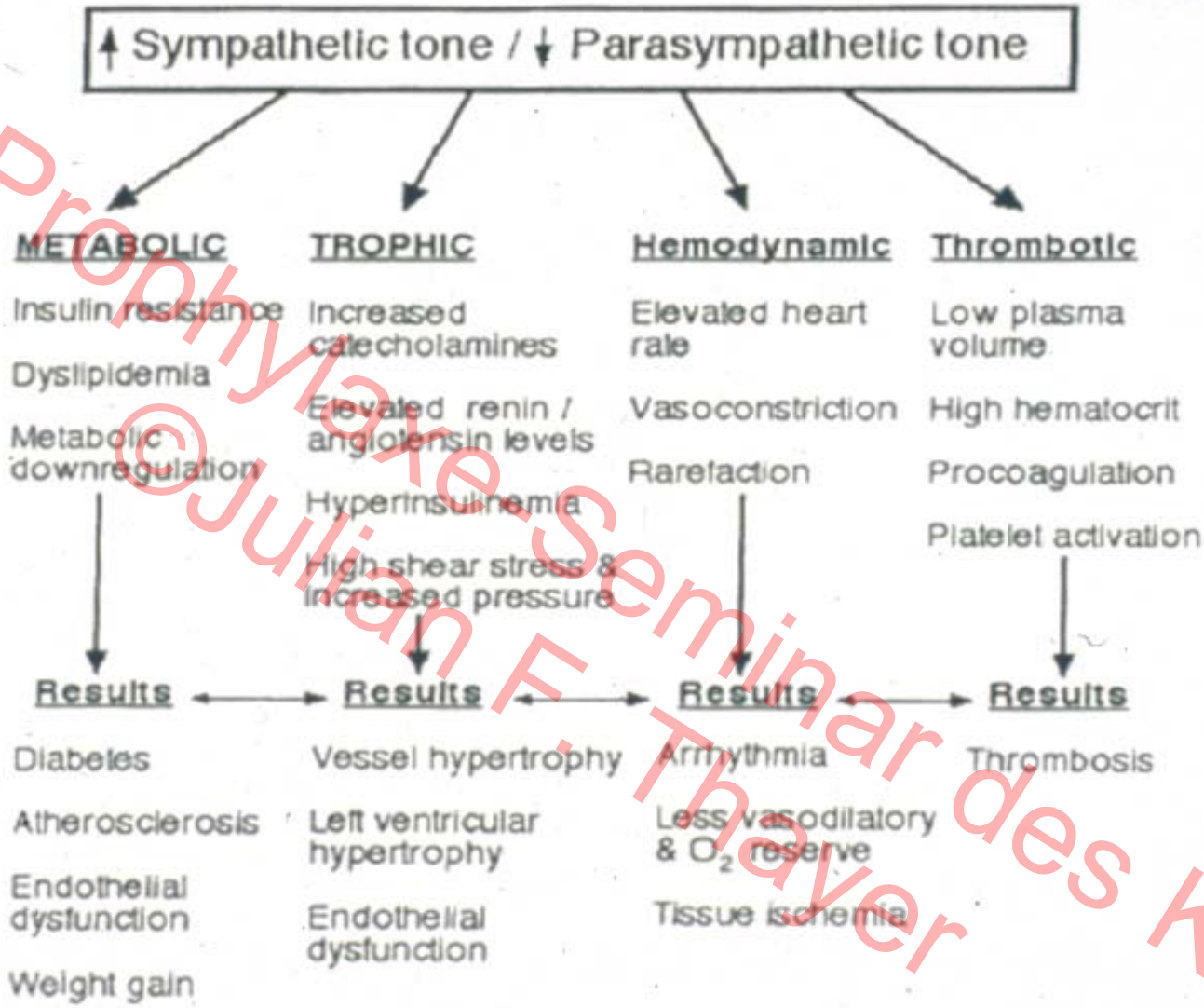
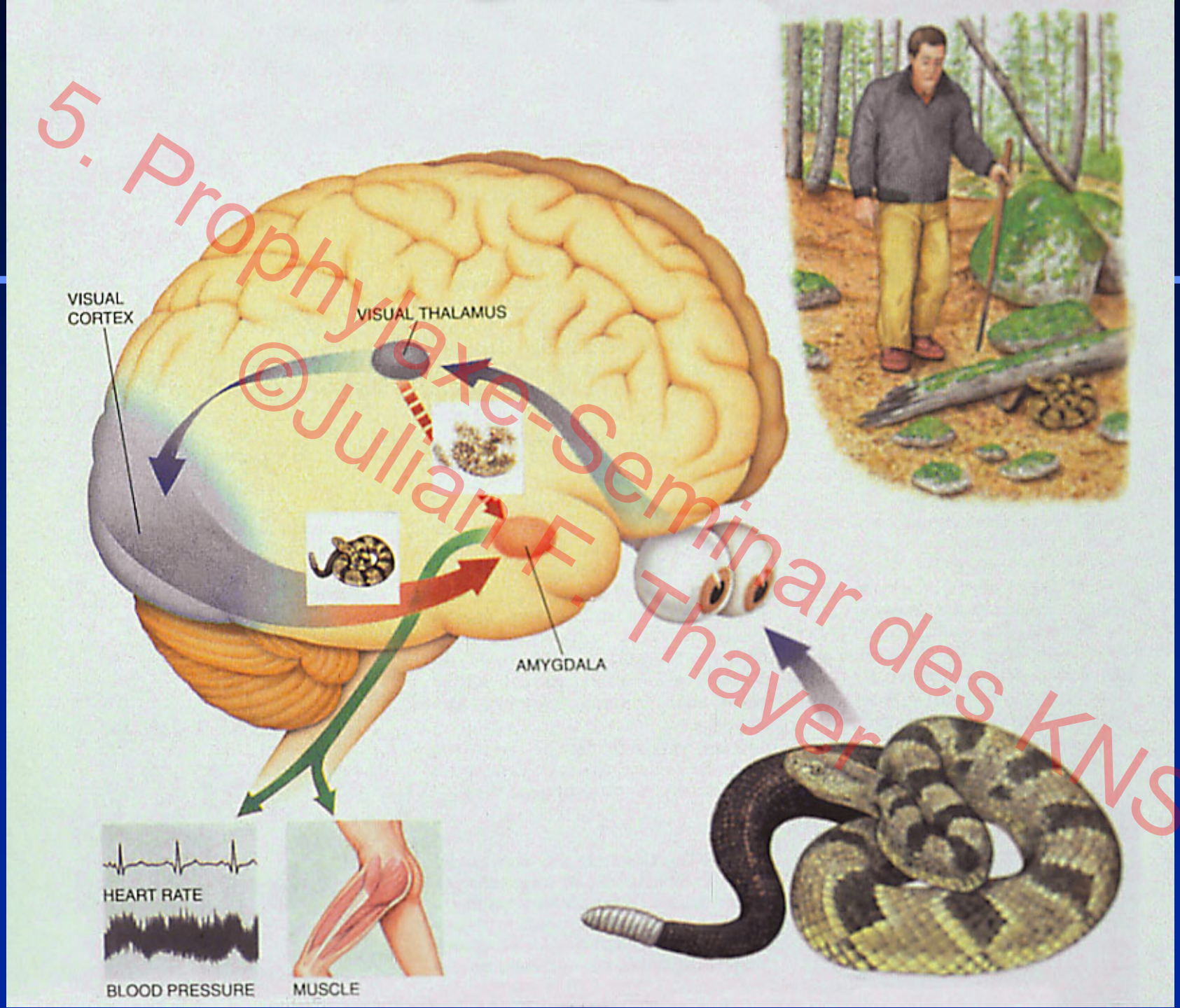


FIGURE 1. *Autonomic imbalance.*

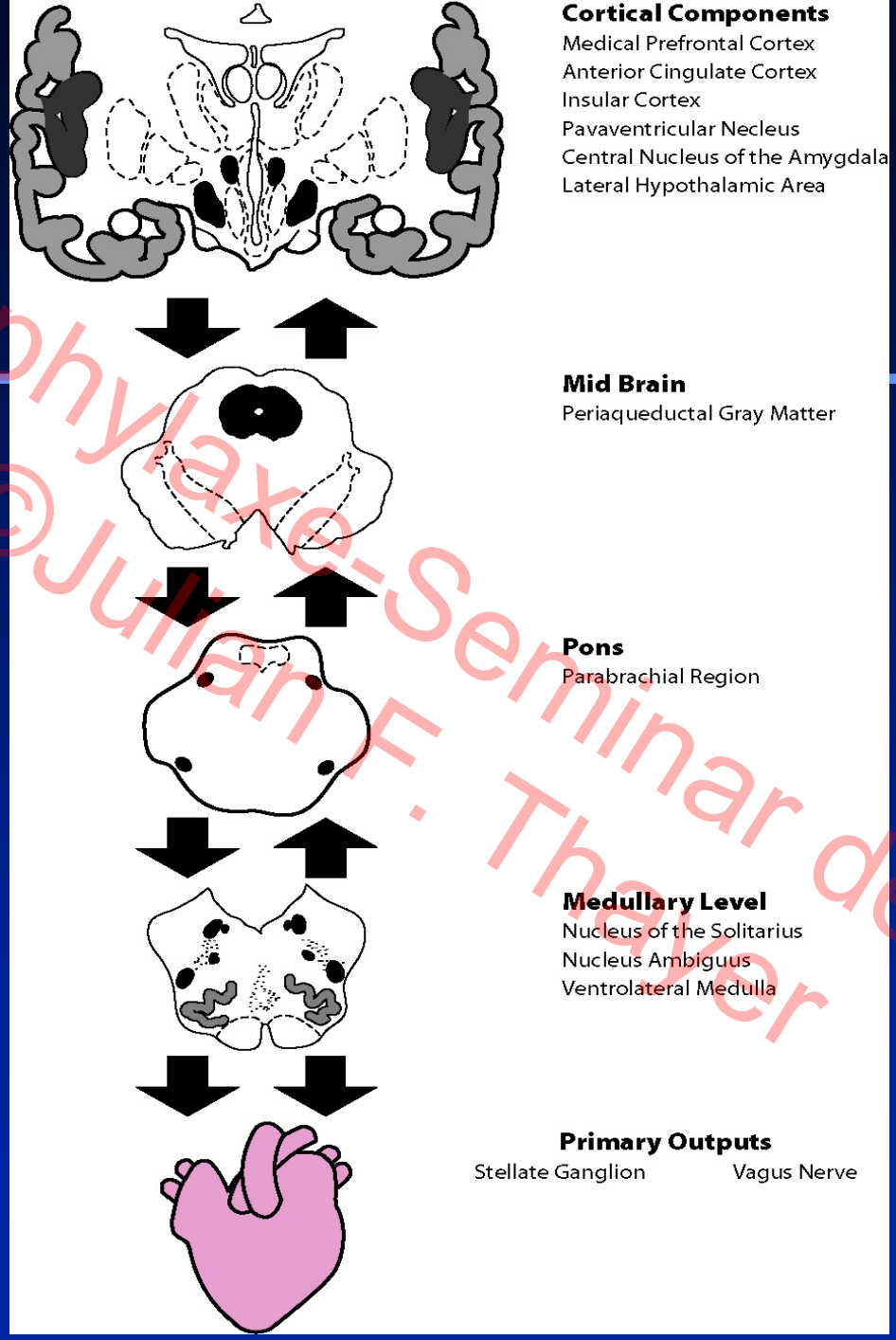


The “Default” Stress Response

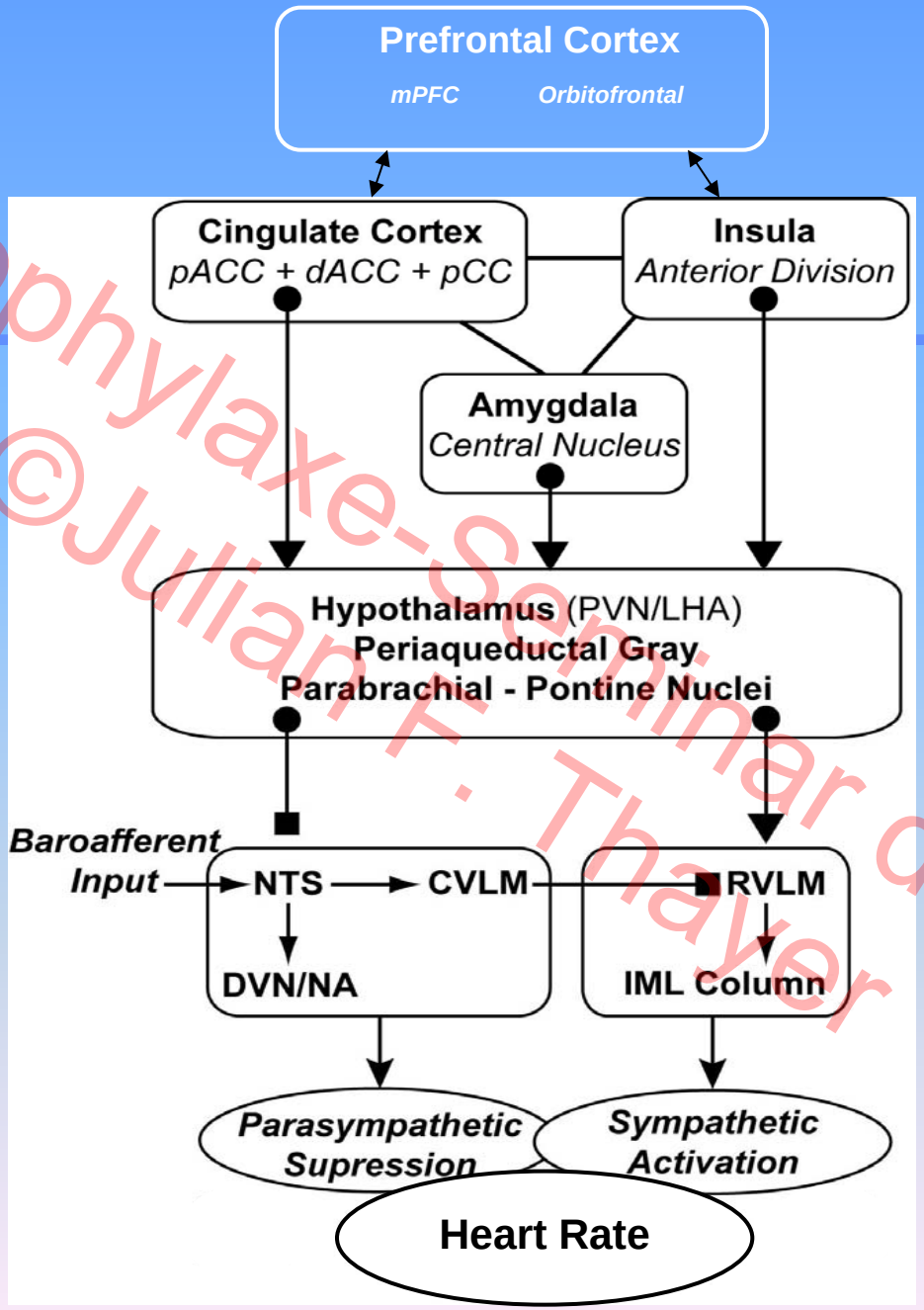
- When in doubt prepare for the worst
- Adaptive response
- Fast, automatic?
- The negativity bias

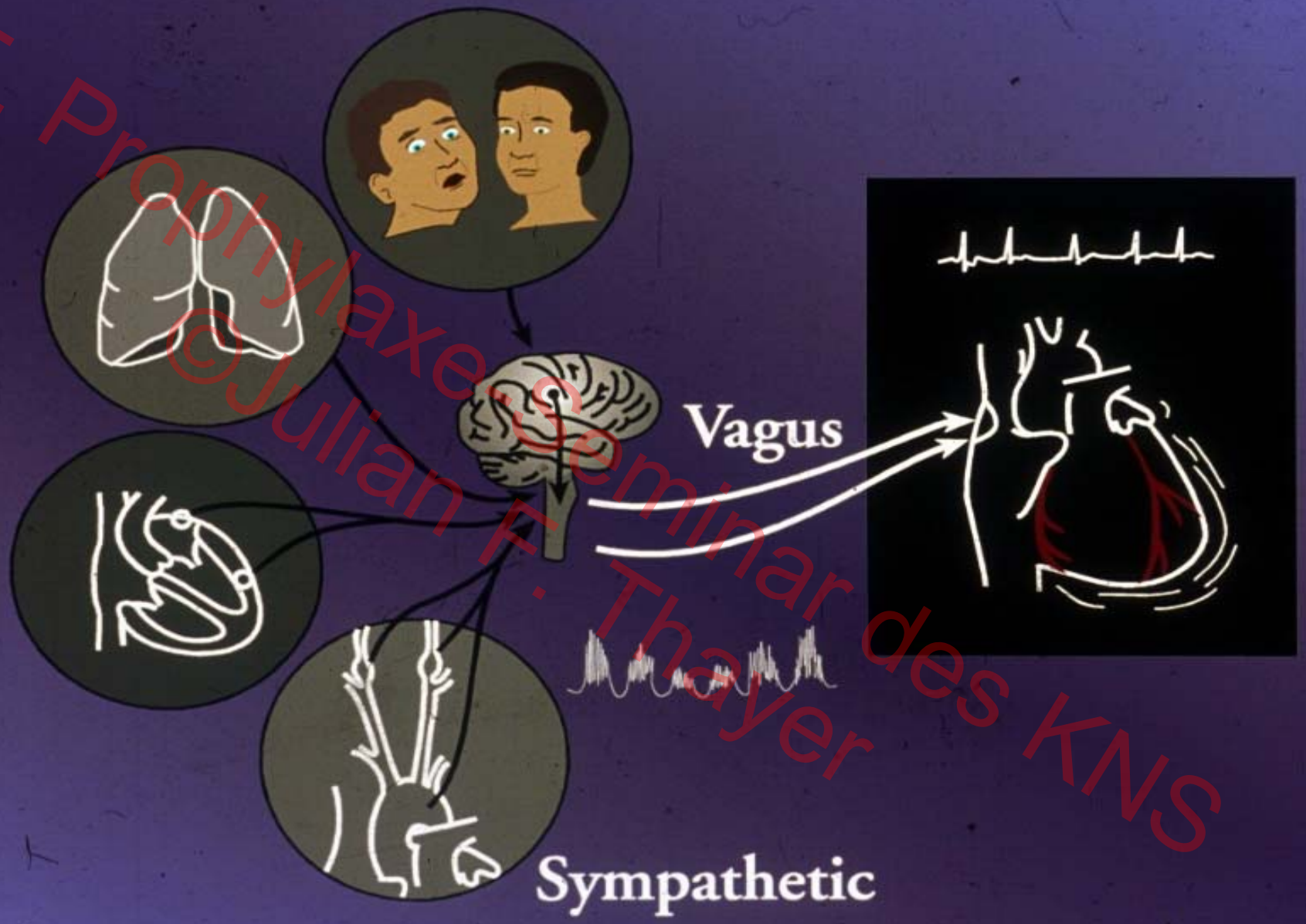
Neurovisceral Integration Model

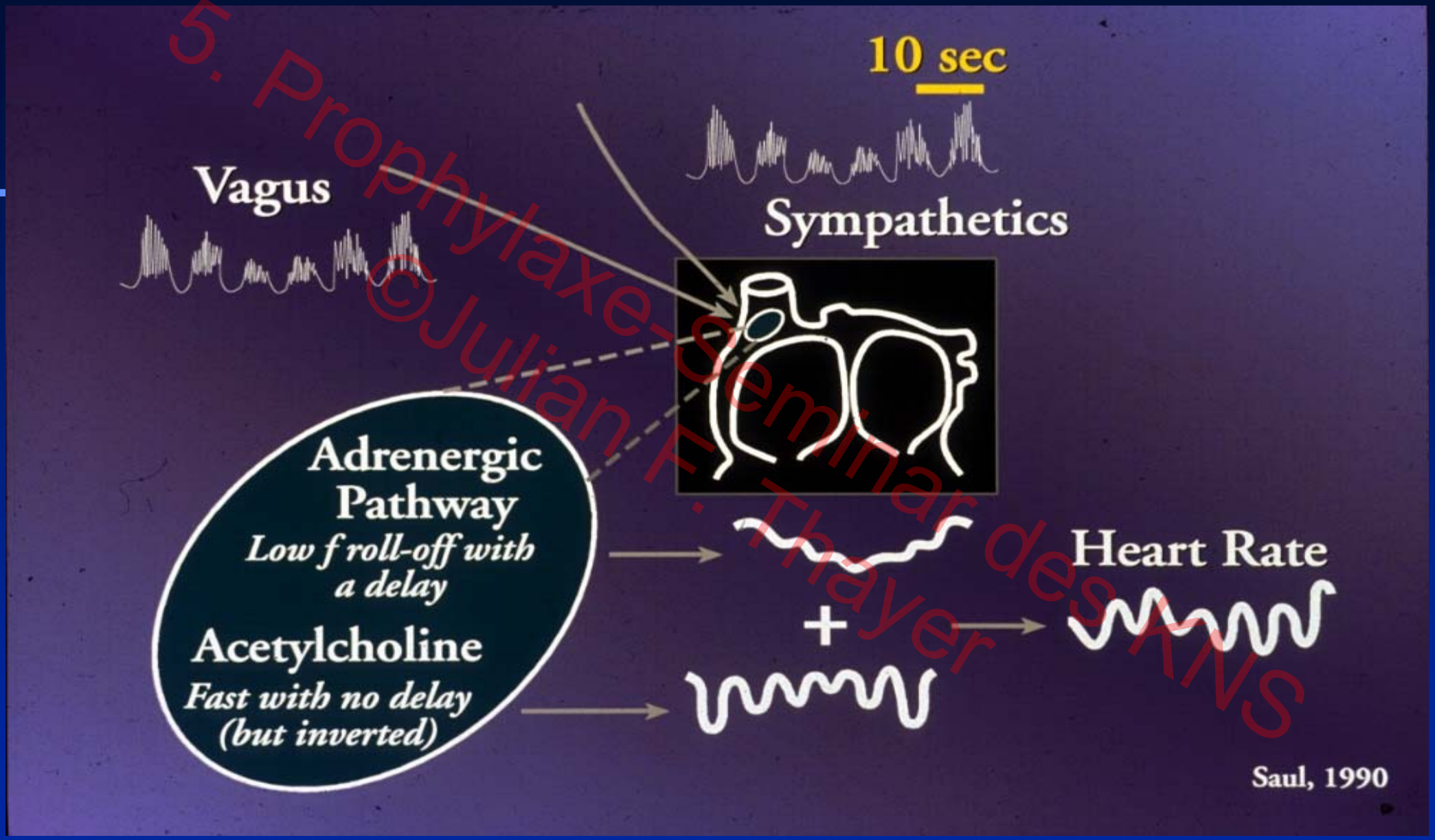
- This neural network can be indexed by heart rate variability
- Higher HRV associated with greater prefrontal inhibitory tone
- Lack of inhibition leads to undifferentiated threat response to environmental challenges (less flexibility)

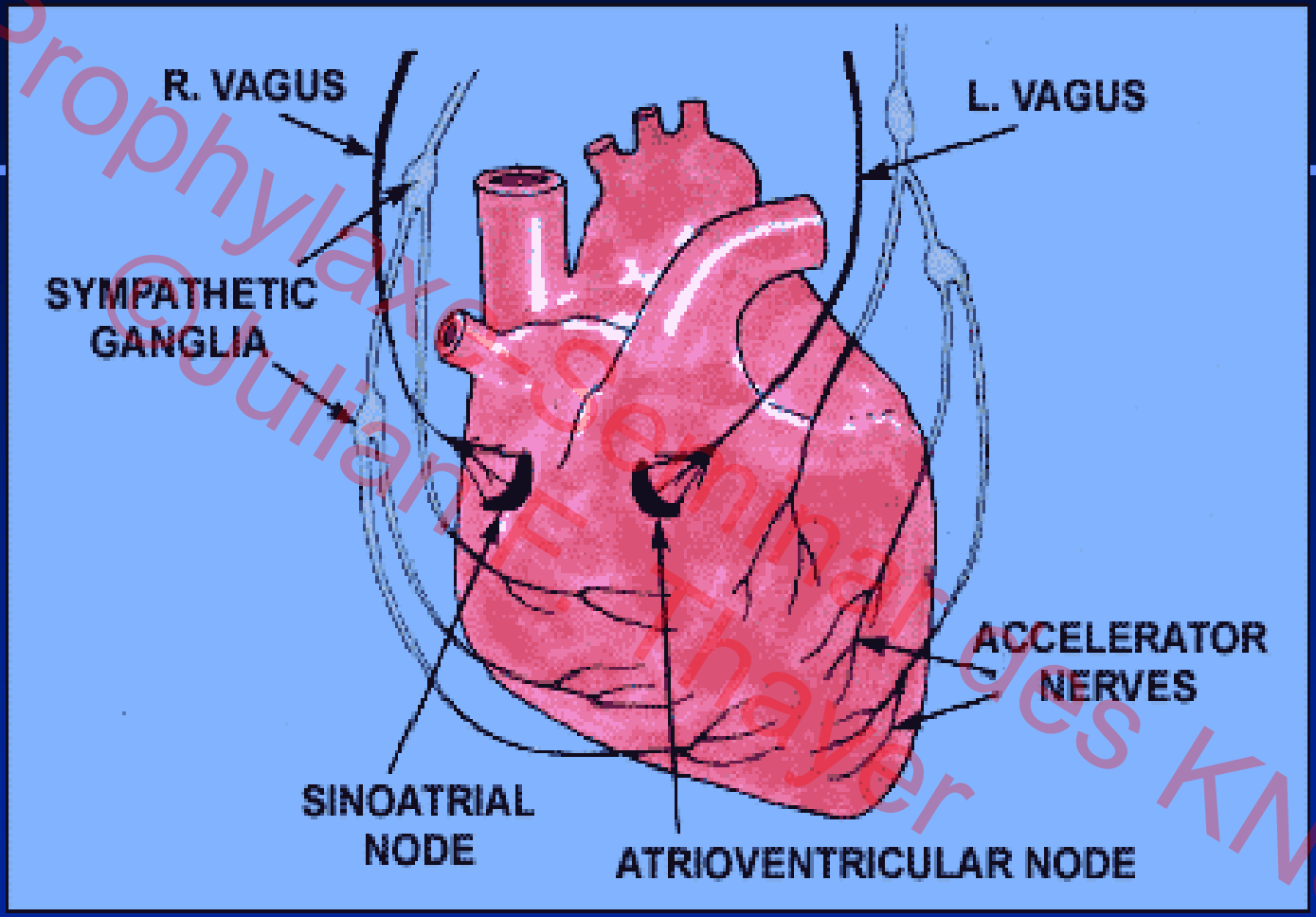


5. Prophylaxe-Seminar des KNS



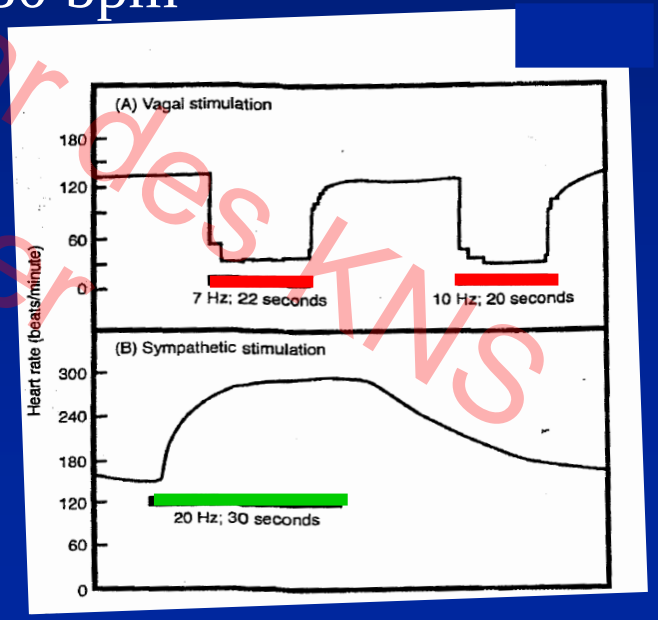






PNS influences:
“what happens in vagus …”

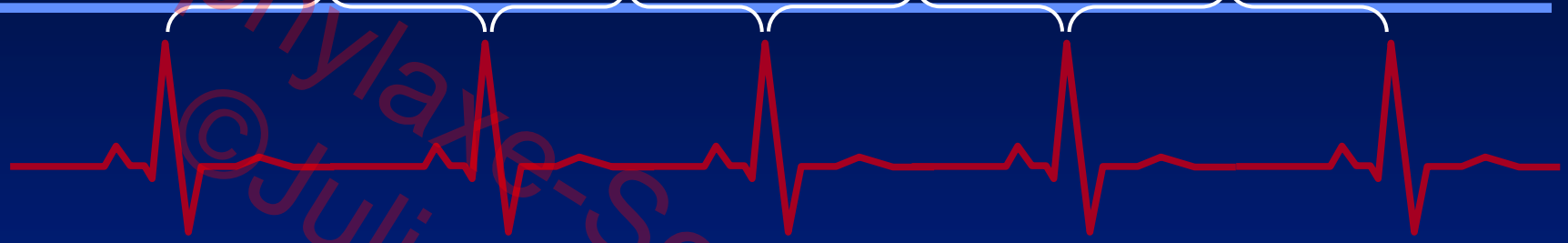
- PNS influences dominate: “vagal tone”[1]
  - intrinsic firing rate of S-A cells: 105 bpm
  - normal resting heart rate: 60–80 bpm [2]
- PNS mediation faster than SNS
  - PNS mediation (ACh): milliseconds
    - rapid action and hydrolysis
  - SNS mediation (NE): seconds

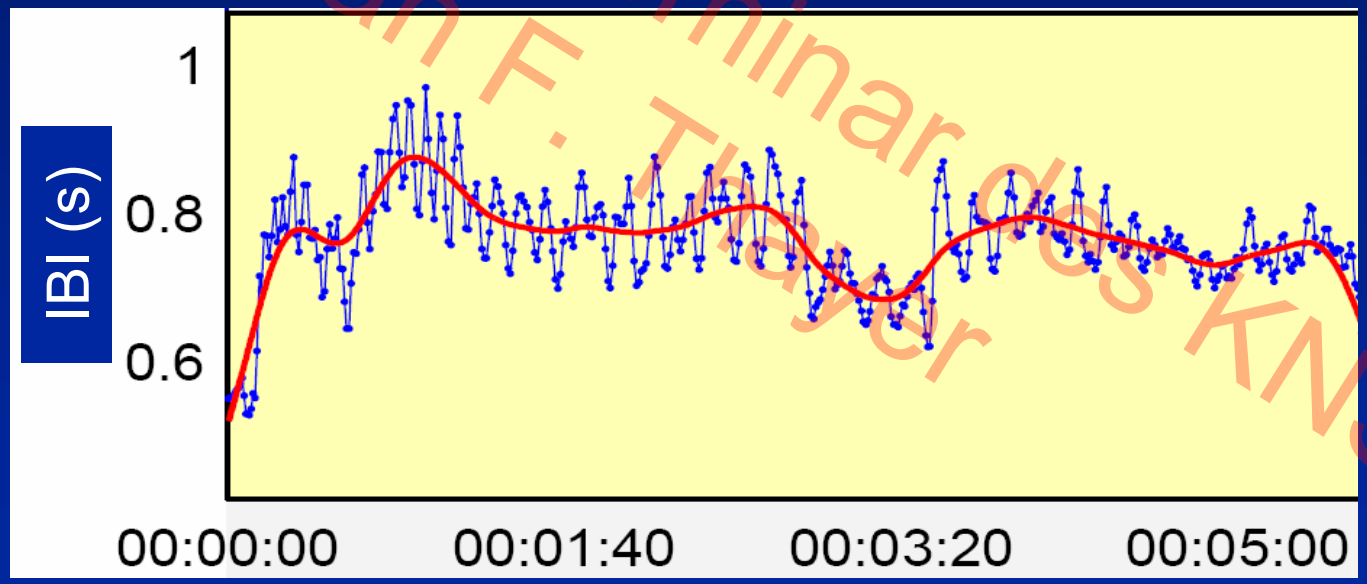


Warner & Cox, 1962

Heart Rate Variability

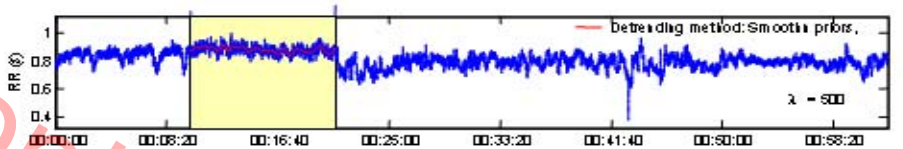
inter-beat interval (IBI): 1000 900 950 980

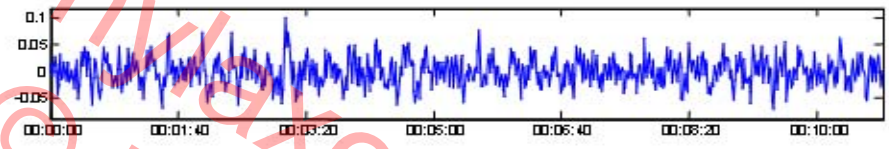


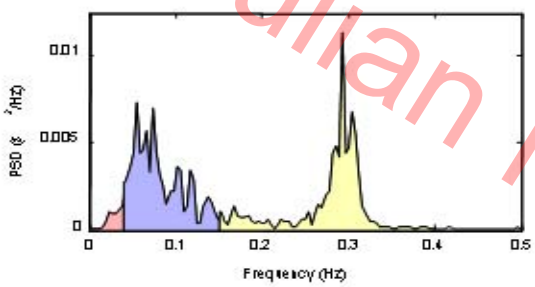


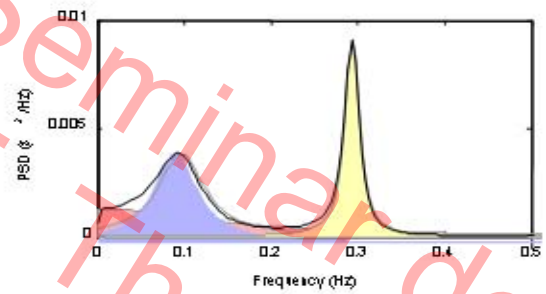
time (min)

QEKG Methods





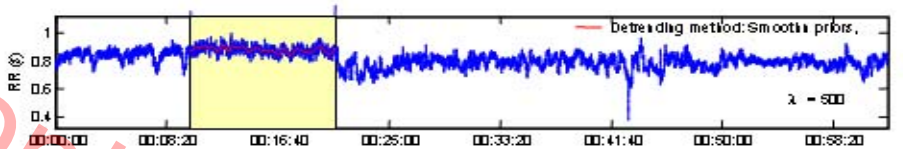


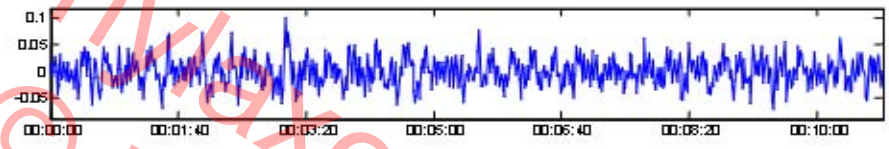


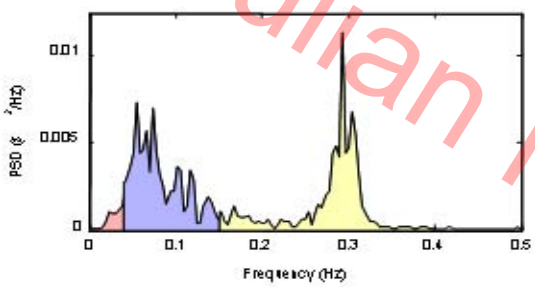
Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0391	23	3.5	
LF (0.04-0.15 Hz)	0.0547	321	49.6	51.4
HF (0.15-0.4 Hz)	0.2930	304	46.9	48.6
Total		648		
LF/HF		1.058		

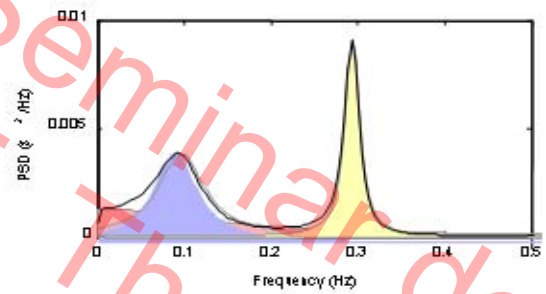
Frequency Band	Peak (Hz)	Power (ms^2)	Power (%)	Power (n.u.)
VLF (0-0.04 Hz)	0.0000	318	33.4	
LF (0.04-0.15 Hz)	0.0977	354	37.2	55.8
HF (0.15-0.4 Hz)	0.2930	281	29.4	44.2
Total		953		
LF/HF		1.263		

QEKG Methods









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HRV and organism health

- An index of physiological health[4]
  - ↓ HRV_{rest} assoc. with ↑ levels of: hypertension, diabetes, cholesterol, obesity, arthritis, cancers
  - Independent predictor of all-cause mortality
- An index of emotional health[5]
  - ↓ HRV_{rest} associated with ↑ depression, anxiety
- An index of attentional processes[6,7,8]
  - HRV ↓ as attentional demands ↑
- An index of cognitive health[6]
  - ↑ HRV_{rest} linked with ↑ accuracy and faster RTs during working memory task

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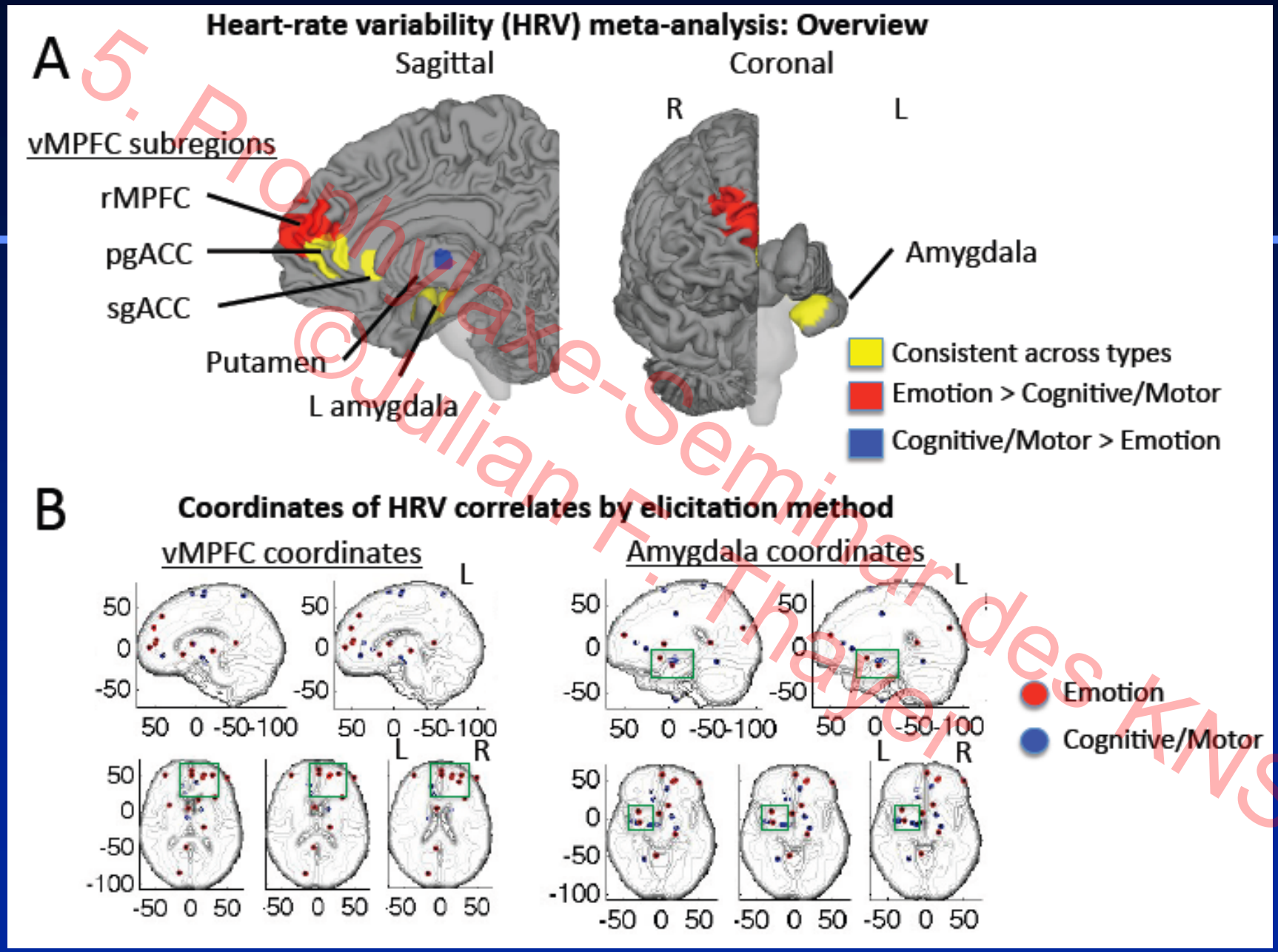
Review

A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health

Julian F. Thayer[a,b,*], Fredrik Åhs[c], Mats Fredrikson[c], John J. Sollers III[d], Tor D. Wager[e]



Resting high-frequency heart rate variability is related to resting brain perfusion

BEN ALLEN,[a] J. RICHARD JENNINGS,[a] PETER J. GIANAROS,[a] JULIAN F. THAYER,[b] AND STEPHEN B. MANUCK[a]

Psychophysiology, •• (2014)

Table 1. *Basic Characteristics of the Whole Sample and Subgroups*

	Whole sample $n = 432$	Men $n = 179$	Women $n = 183$	European Americans $n = 362$	African Americans $n = 61$
Age (years)	42 (7)	41 (7)	43 (6)*	42 (7)	44 (6)*
Body mass index	26 (5)	26 (4)	25 (5)*	26 (4)	29 (5)***
Systolic BP (mmHg)	114 (11)	116 (10)	111 (10)*	113 (11)	119 (10)***
Current smoker (%)	14.8	13.4	13.7	13.5	23.0
Ln HF-HRV	6.10 (1.34)	6.07 (1.32)	6.12 (1.26)	6.10 (1.29)	6.28 (1.57)
Years of schooling	16 (2)	17 (2)	16 (2)	17 (2)	15 (2)***
Median household income (k)	35 (6)	36 (6)	35 (6)	36 (6)	31 (6)***
Kilocalories burned per week	2,950 (2,441)	3,392 (2,922)	2,651 (1,898)**	3,055 (2,422)	2,795 (2,834)*

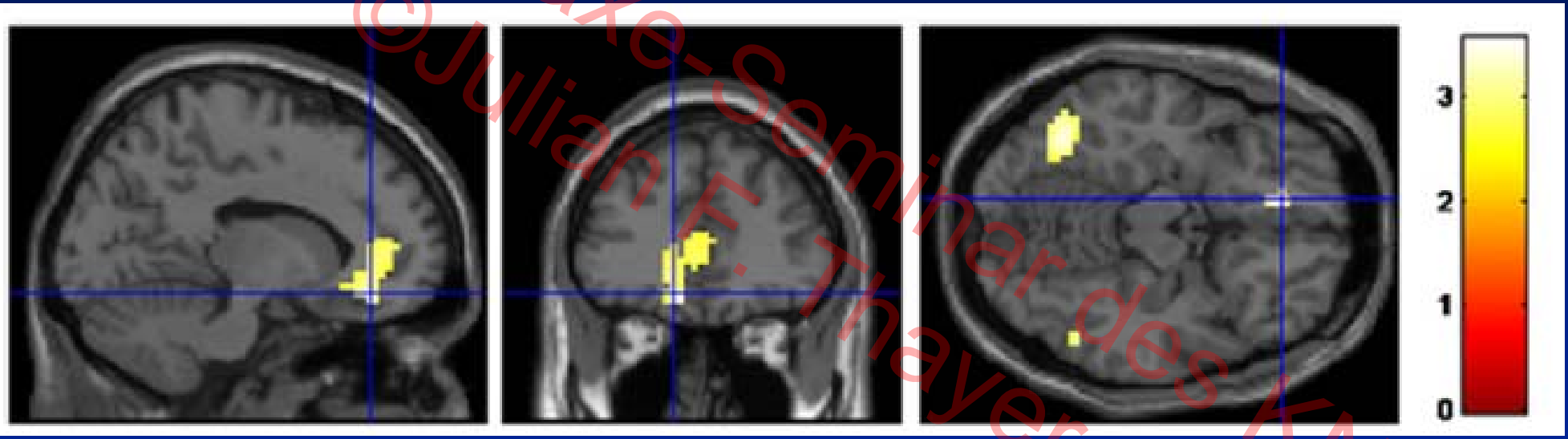
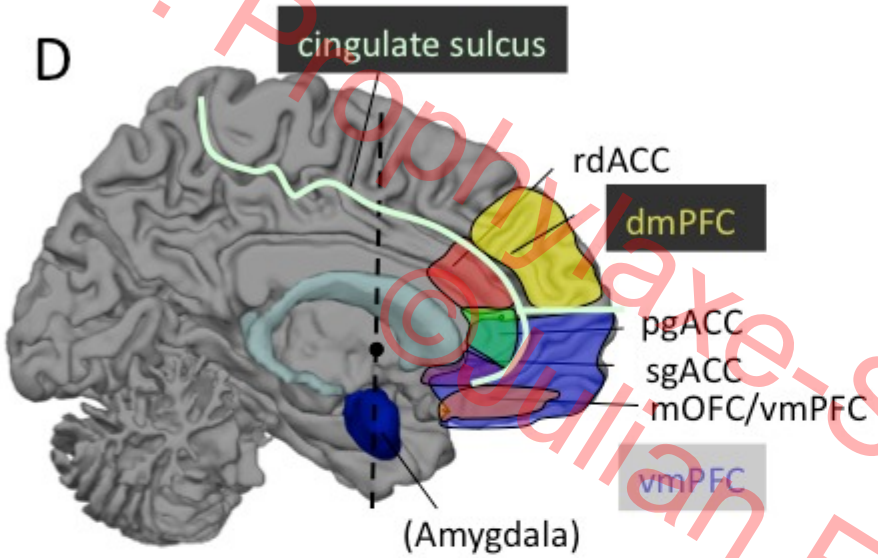


Figure xxx. Subdivisions of the medial prefrontal cortex

Medial prefrontal regions associated with emotion and social cognition



Functional categorization according to Amodio and Frith, 2006

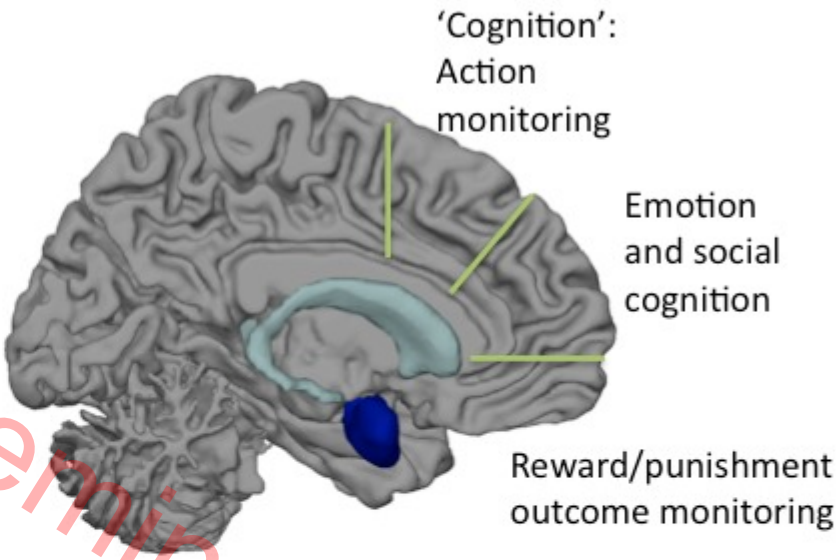
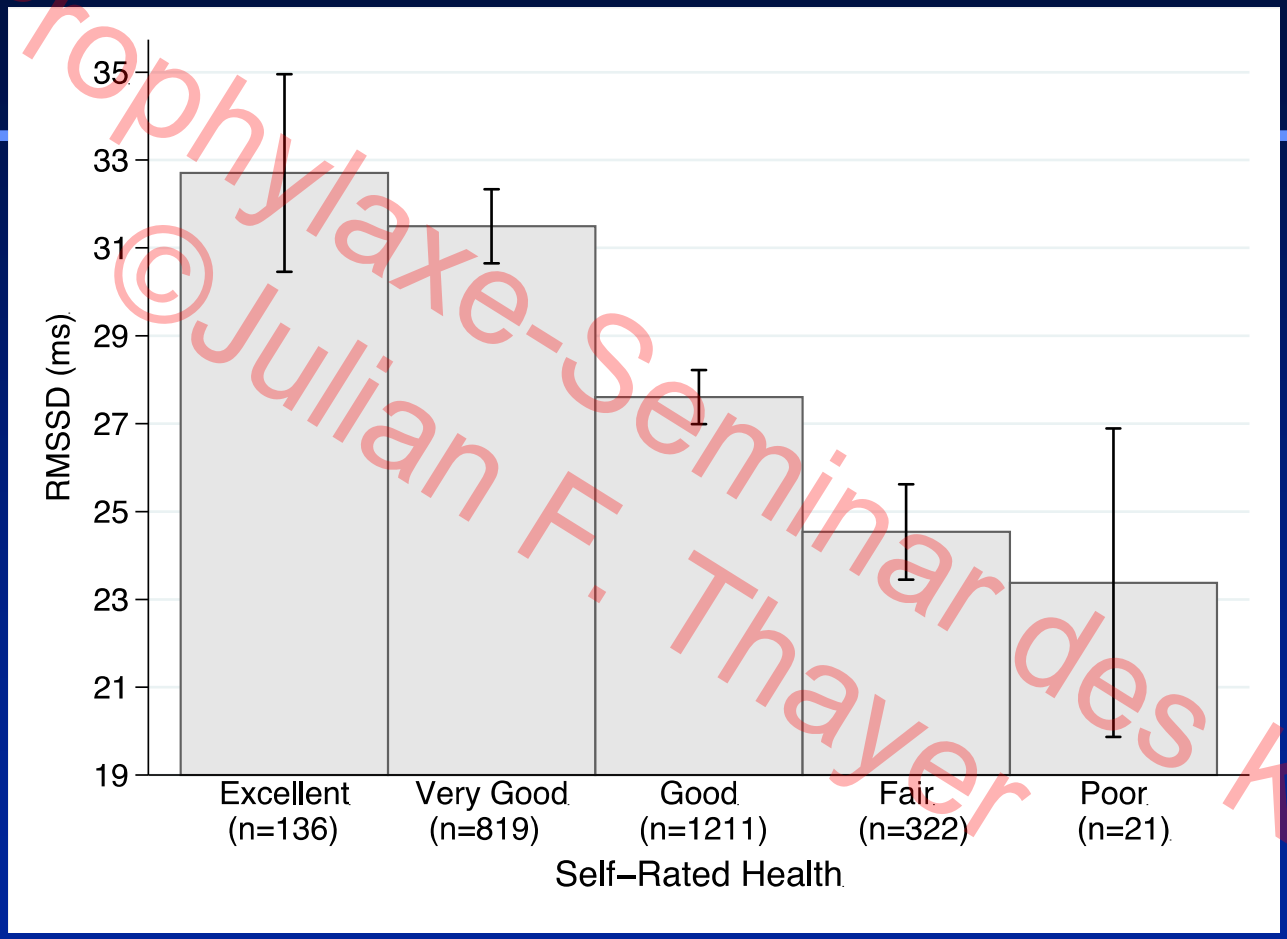
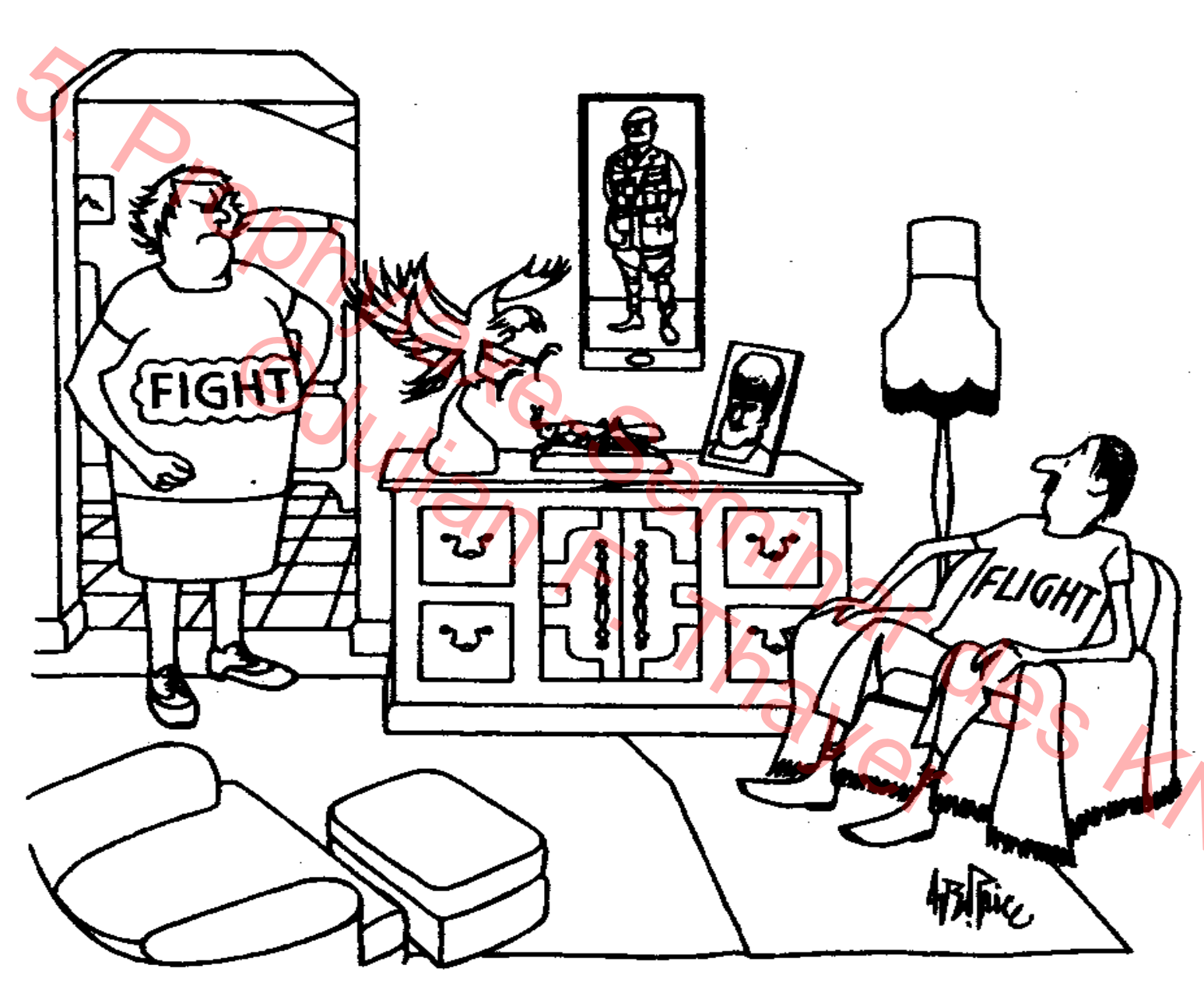
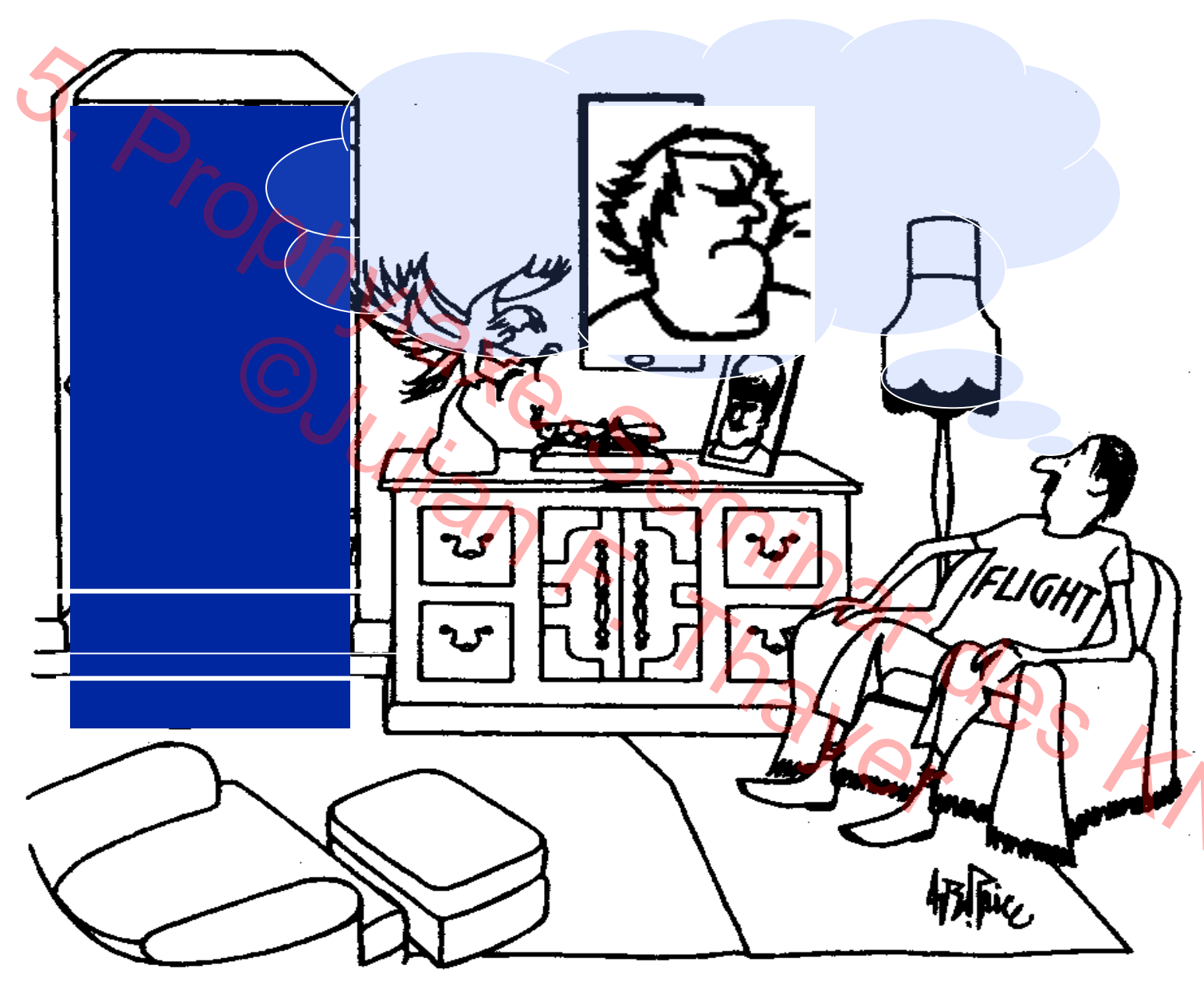


Figure 1 Mean RMSSD and self-rated health (error bars 95% CI)

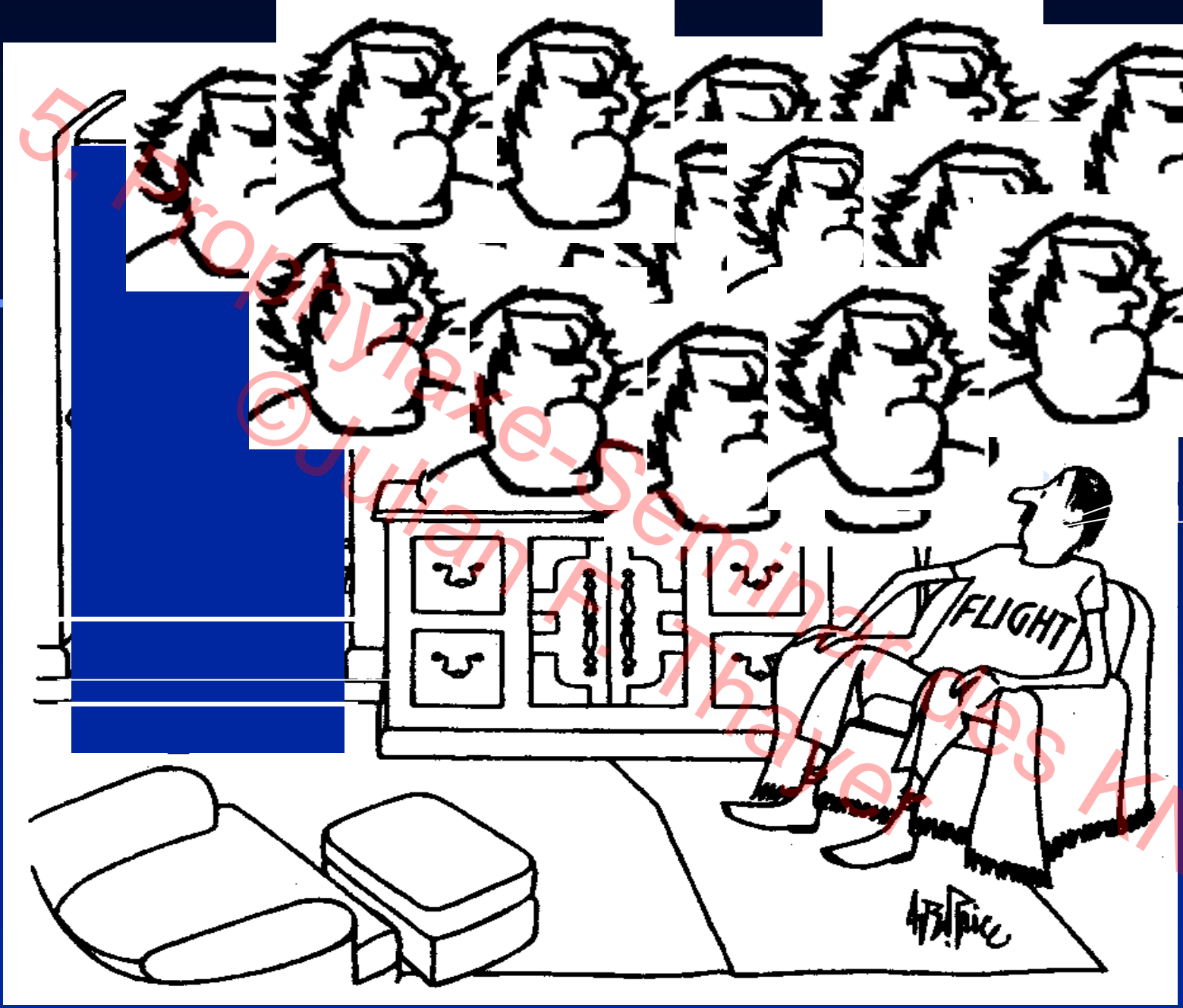




Human stress is…..



Perseverative cognition…..

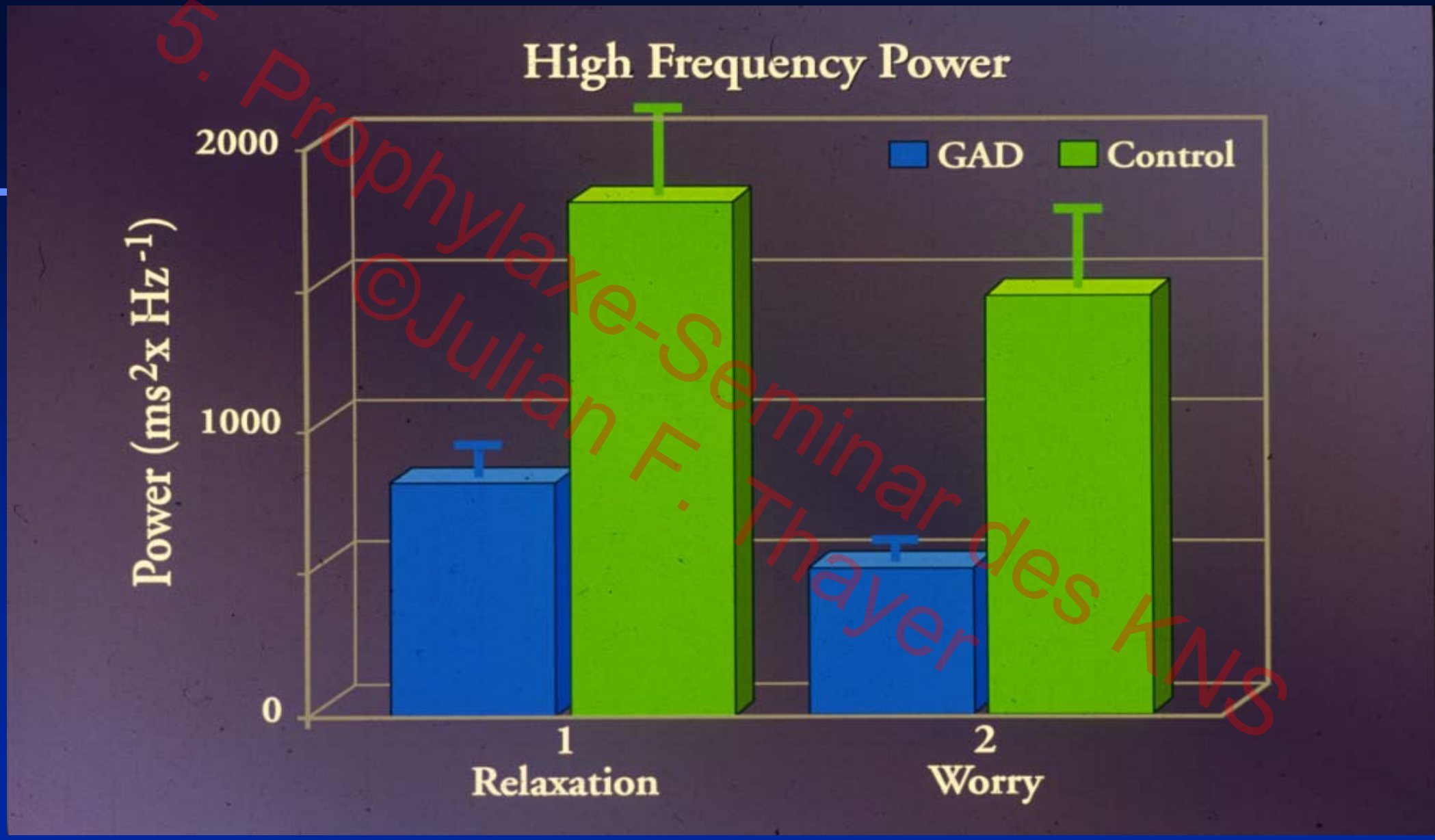


Help…

Extreme⟶ anxiety disorder...

Autonomic Characteristics of Generalized Anxiety Disorder and Worry

Julian F. Thayer, Bruce H. Friedman, and Thomas D. Borkovec



High-frequency heart rate variability during stress correlates with anterior cingulate regional cerebral blood flow in patients with social phobia

Fredrik Åhs
John Sollers
Tomas Furmark
Julian Thayer
Mats Fredrikson

UPPSALA UNIVERSITY

Experimental set up

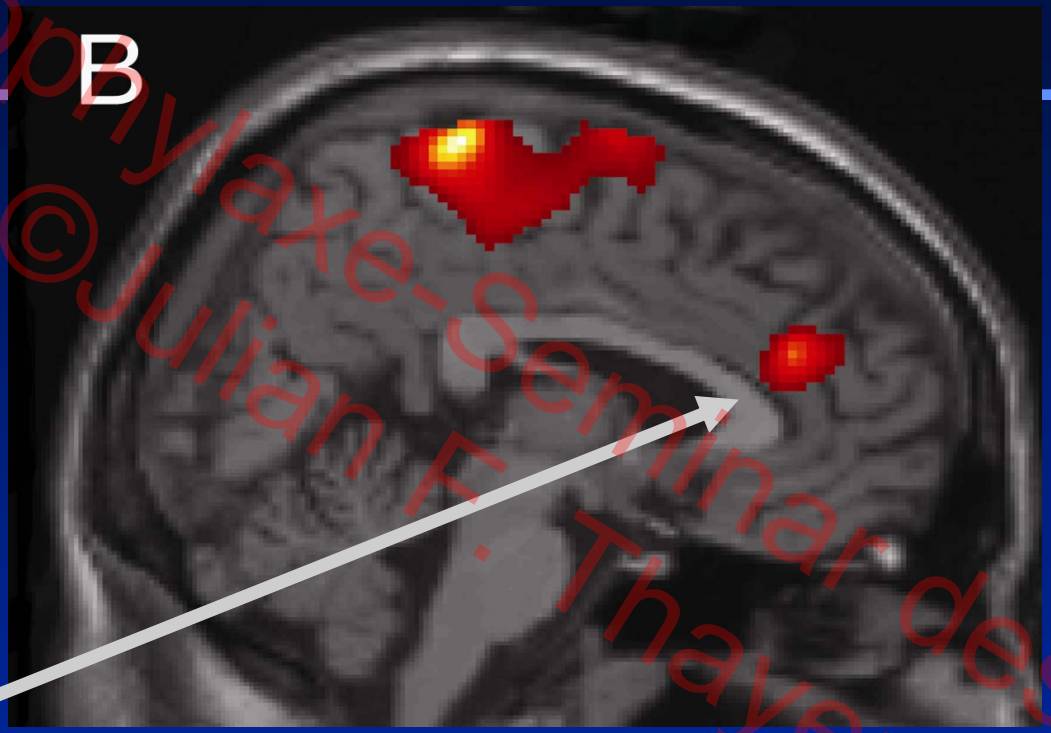
Audience waiting

Audience assembled

During speech

Cortisol sampling after speech

Negative correlation between cortisol and rCBF in the ACC



The arrow shows the negative correlation cluster in the ACC. Statistical maximum at the Talairach coordinate x = 4, y = 38, z = 18, Z = 3.56 , p = 0.02 corrected

UPPSALA UNIVERSITY

Ahs, et al., Psychosomatic Medicine, 2006

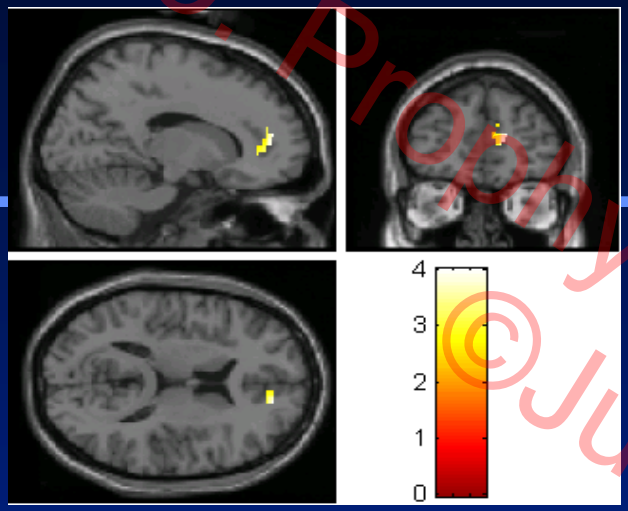
Aim

Given that the anterior cingulate is involved in negative feed back control of the HPA-axis we expected a positive relation to vagal tone as measured by high frequency heart rate variability in this brain region.

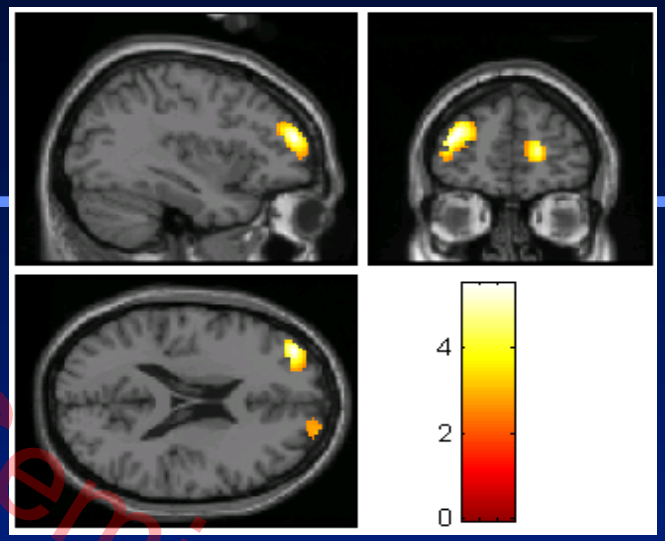
Methods

- N=29
- Regional cerebral blood flow measured 15O-water positron emmision tomography
- High frequency HRV was extracted from the R-R intervals in the ECG during speech
- Statistical analysis in SPM2
- ACC ROI defined in WFU PickAtlas
- FWE-correction for multiple comparison

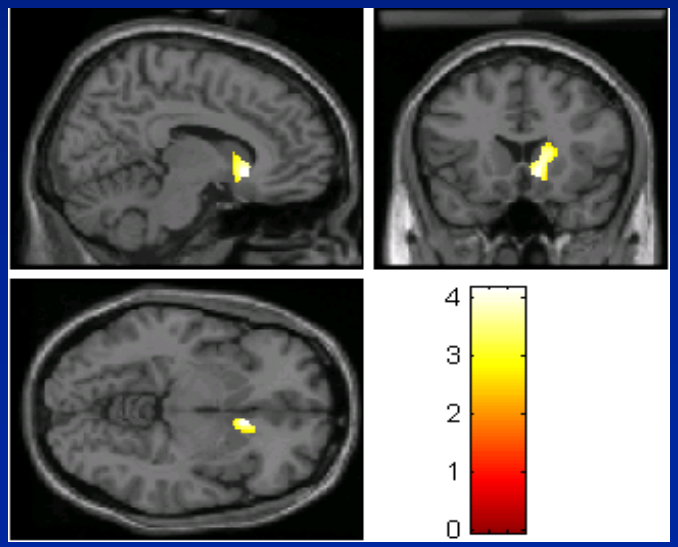
ACC



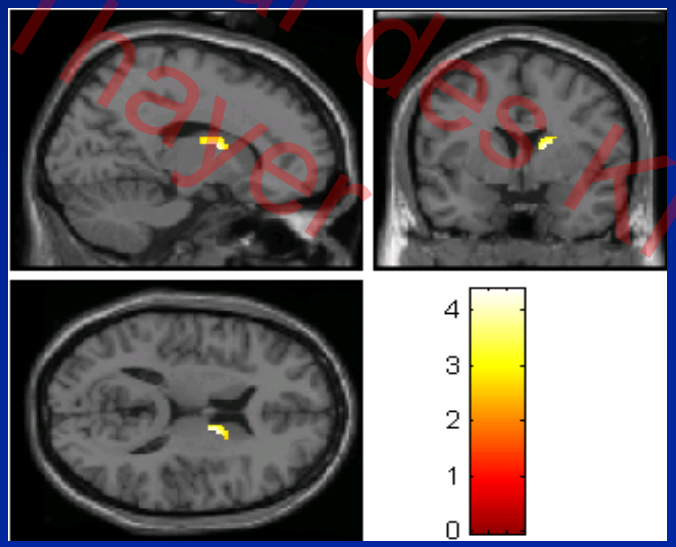
BA10/46 (46 in left hemisphere only)



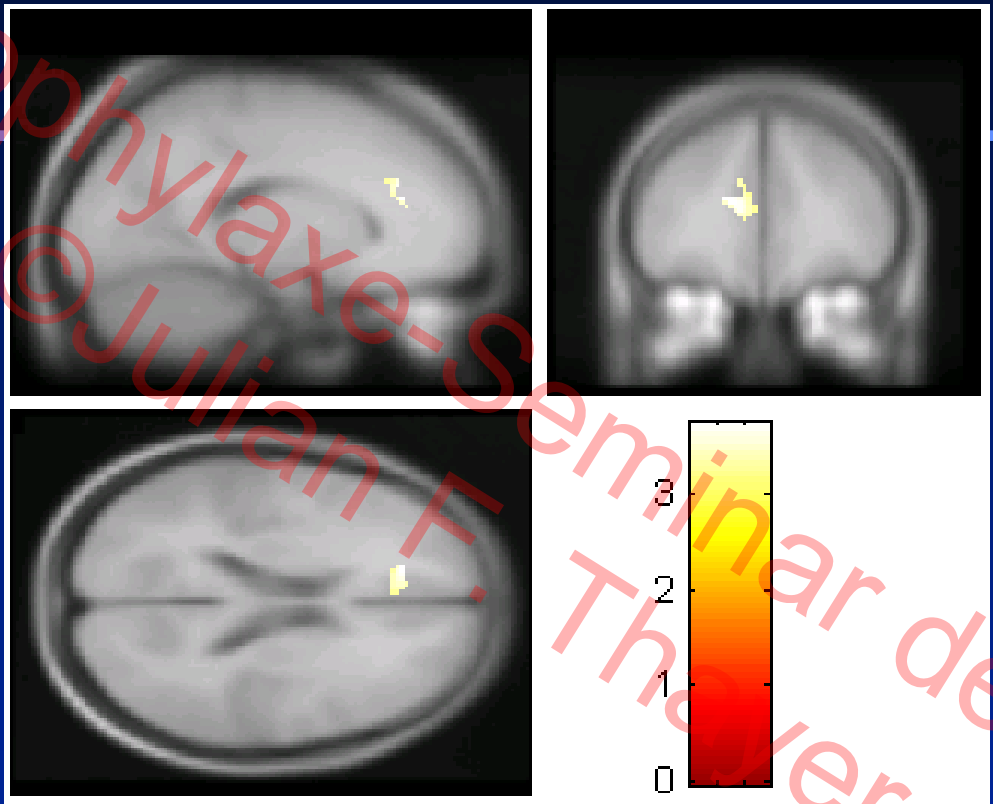
Caudate



Men stronger positive correlation than women in the caudate



Negative correlation between state anxiety and rCBF in the ACC



The maximum is in the Talairach coordinate x = -16, y = 38, z = 16, Z=3.54, p=0.04 corrected

Conclusion

The supra-genual anterior cingulate might be a control region for vagal tone during social stress.

Activity in the anterior cingulate cortex reflects processes involved in the emotion congruent control over bodily states and mapping of emotional states.

Why SLEEP ?!

* Major restorative period (1/3 of life)

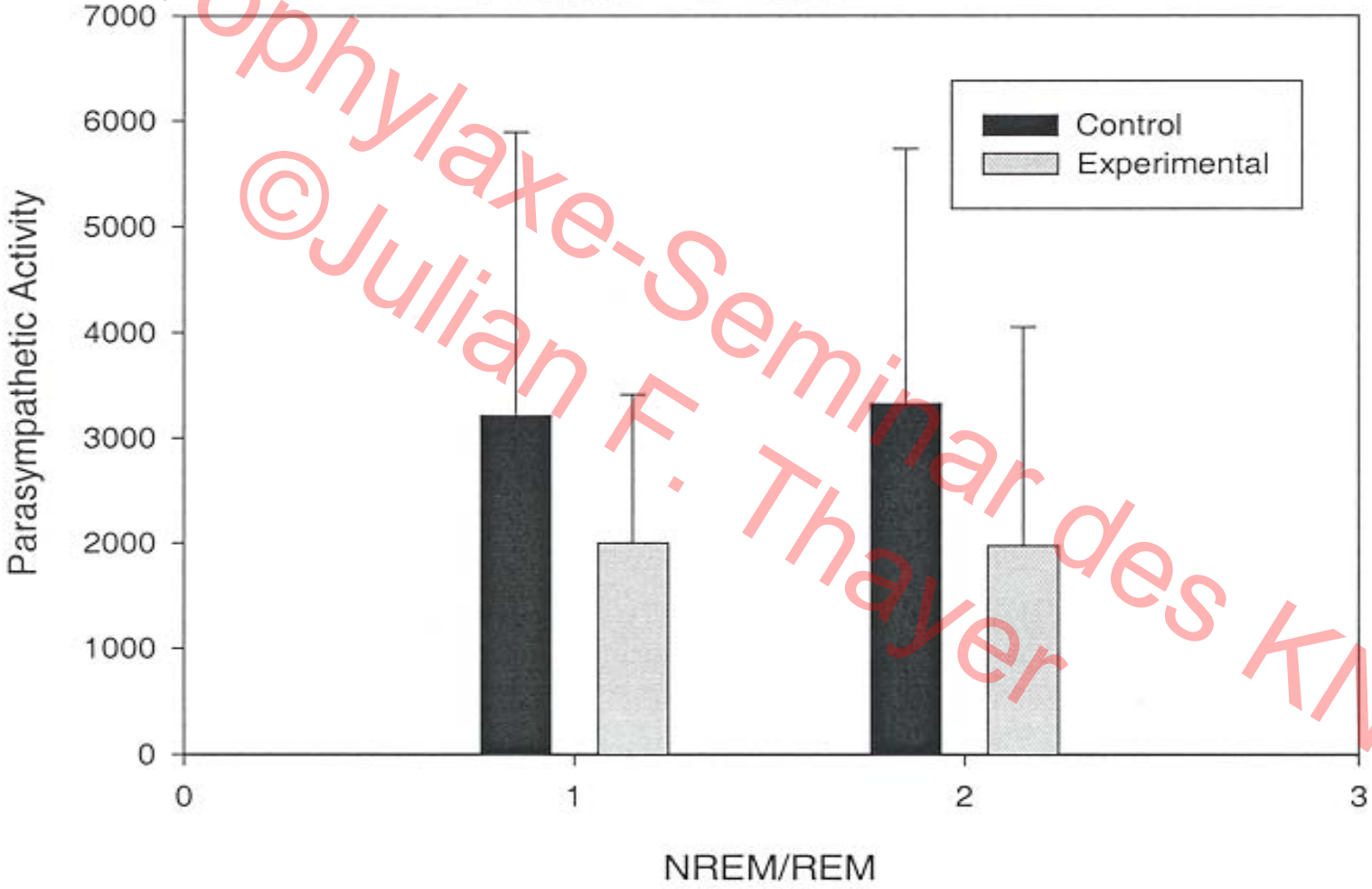
• If stress responses are prolonged during sleep, than sleep = major **mediator** stressors → organic disease

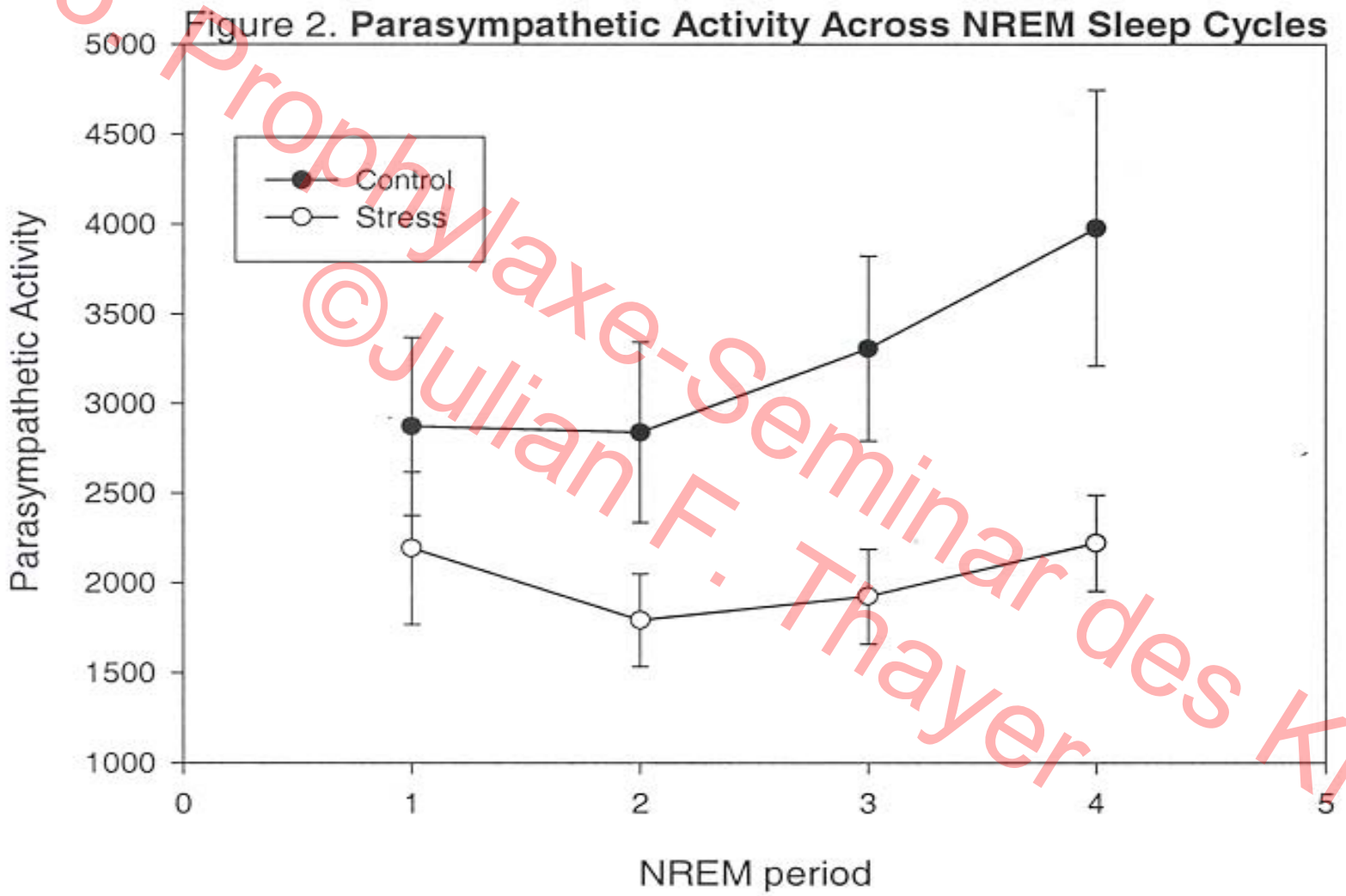
Acute Stress Affects Heart Rate Variability During Sleep

Martica Hall, PhD, Raymond Vasko, PhD, Daniel Buysse, MD, Hernando Ombao, PhD, Qingxia Chen, MS, J. David Cashmere, BS, David Kupfer, MD, and Julian F. Thayer, PhD

Figure 1. **Mean and Std Dev of Parasympathetic Activity for Control vs. Experimental Group During NREM and REM**

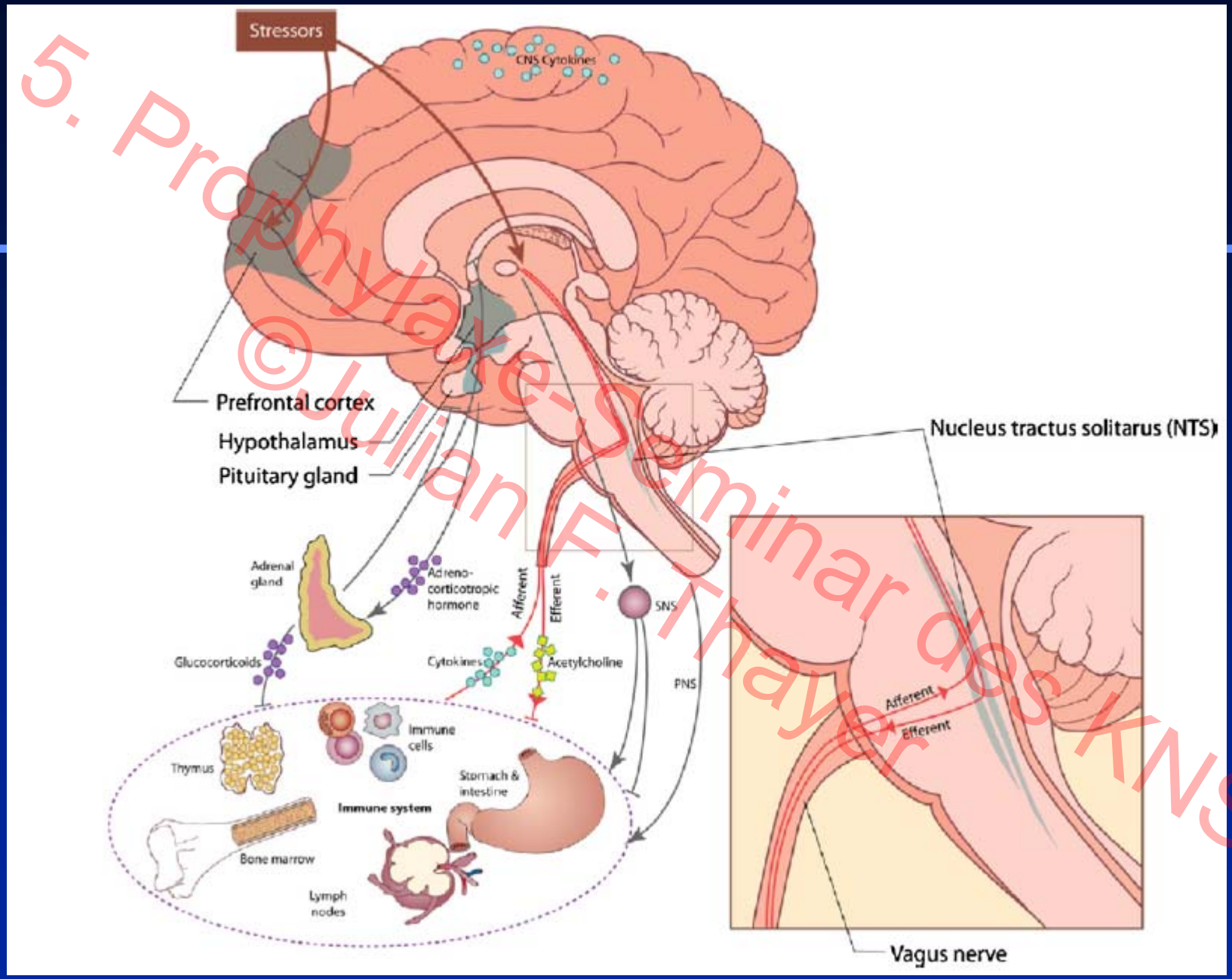
1--NREM 2--REM





Inflammation and Autonomic Imbalance Models are Related

- Proinflammatory cytokines (e.g., IL-6) are inhibited by acetylcholine and parasympathetic tone
- Proinflammatory cytokines under tonic inhibitory control via the vagus
- Helps to explain general health benefit of exercise and physical activity



The Cholinergic Anti-inflammatory Pathway

- Efferent activity in the vagus nerve leads to acetylcholine release in the reticuloendothelial system including the liver, heart, spleen, and GI tract
- Acetylcholine interacts with nicotinic ACh receptors on tissue macrophages which inhibit release of TNF, IL-1, HMGB1 but not IL-10 (Tracey, Nature, 2002)

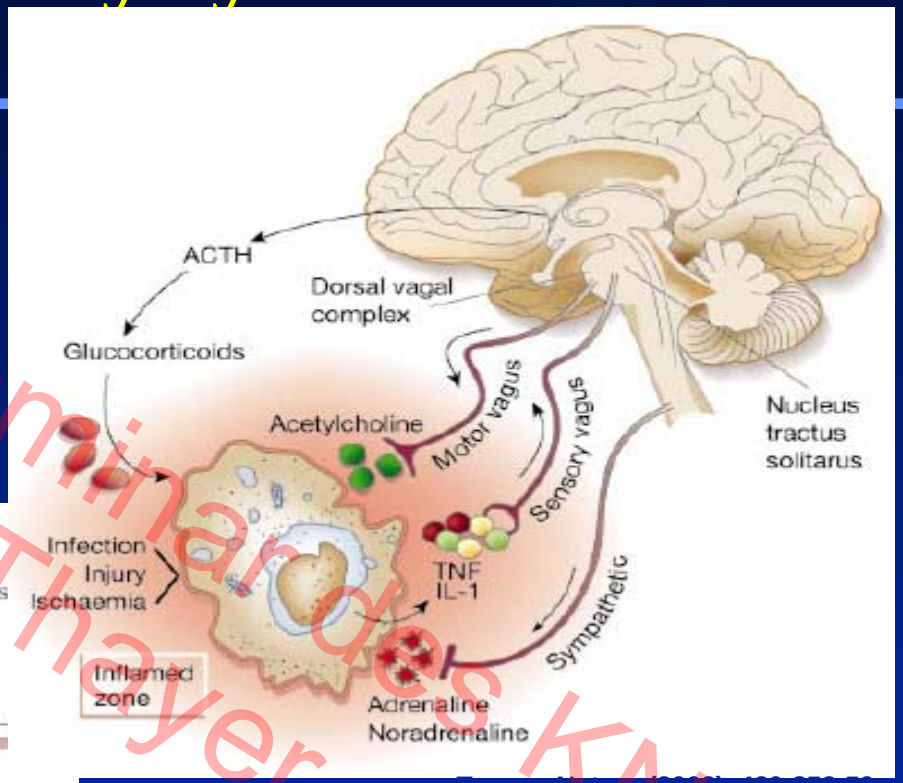
Involved regulatory systems

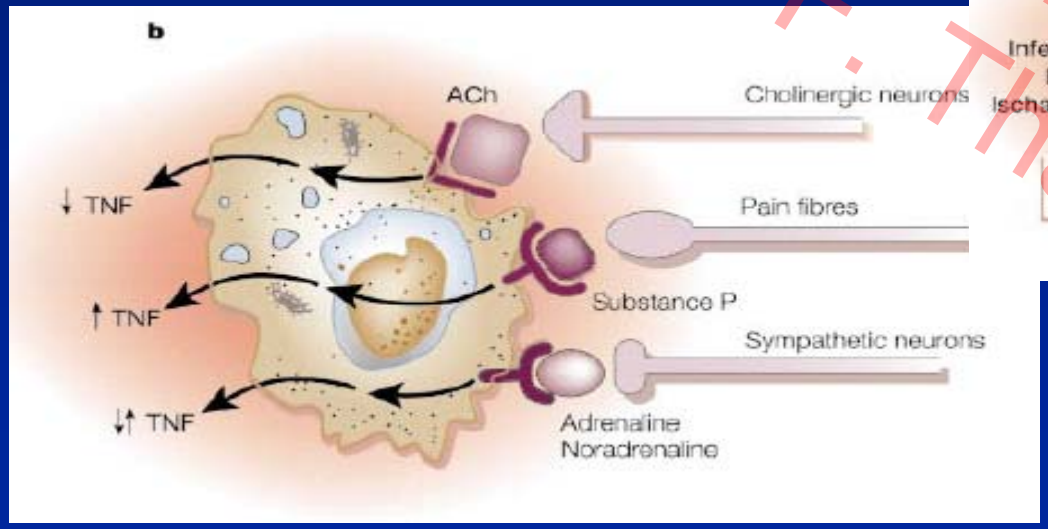
Vegetative Nervous System

- Parasympathetic NS
- Sympathetic NS

Endocrine System (HPA)

- Cortisol





Original Article

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Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults

J. F. Thayer[1,2] & J. E. Fischer[2]

HRV and CRP

- Large study of airplane factory workers in southern Germany
- 24 hr HRV –RMSSD time domain index
- High sensitivity CRP
- Adipose tissue major source of IL-6 which is potent stimulus for hepatic CRP synthesis

	Men	Women	*P*-value
n	545	66	
Age (years)	**42.3 (11.0)**	**34.4 (12.6)**	**<0.001**
Smokers (*n*, %)	142 (26)	24 (36)	0.07
History of hypertension (*n*, %)	75 (14)	8 (12)	0.72
History of myocardial infarction (*n*, %)	4 (0.7)	0 (0)	0.48
Medication with statins (*n*, %)	16 (2.9)	0 (0)	0.16
Diabetes insulin dependent (*n*, %)	7 (1.3)	1 (1.5)	0.87
Diabetes any type (*n*, %)	10 (1.8)	1 (1.5)	0.86
Systolic blood pressure (mmHg)	**124 (14)**	**114 (14)**	**<0.001**
Diastolic blood pressure (mmHg)	**81 (10)**	**75 (9.7)**	**<0.001**
Body-mass-index (kg m^{-2})	**26.5 (3.5)**	**24.1 (4.9)**	**<0.001**
Cholesterol (mg dL^{-1})	**216 (43)**	**204 (43)**	**0.04**
High-density lipoprotein (mg dL^{-1})	**53 (11.9)**	**67 (15.8)**	**<0.001**
Low-density lipoprotein (mg dL^{-1})	**134 (38)**	**116 (39)**	**0.001**
Triglycerides (mg dL^{-1})	157 (122)	125 (162)	0.13
C-reactive protein (mg dL^{-1})	**0.18 (0.30)**	**0.43 (0.75)**	**0.01**
Haematocrit (%)	**45.7 (2.4)**	**41.6 (2.7)**	**<0.001**
Habitual physical activity (days/week)	2.7 (1.05)	2.63 (1.11)	0.60
Urinary norepinephrine (per gram urinary creatinine)	**15.9 (8.5)**	**20.7 (11.1)**	**0.001**
White blood cell count	5.8 (1.6)	6.2 (1.5)	0.84
pNN50 (%)	0.15 (.11)	0.14 (.08)	0.28
RMSSD (ms)	38.9 (14.5)	37.8 (12.6)	0.50

pNN50, per cent of interbeat interval differences >50 ms; RMSD, root mean square of successive differences. Significant gender differences are given in bold.

Table 3 Partial correlation coefficients with C-reactive protein and RMSSD

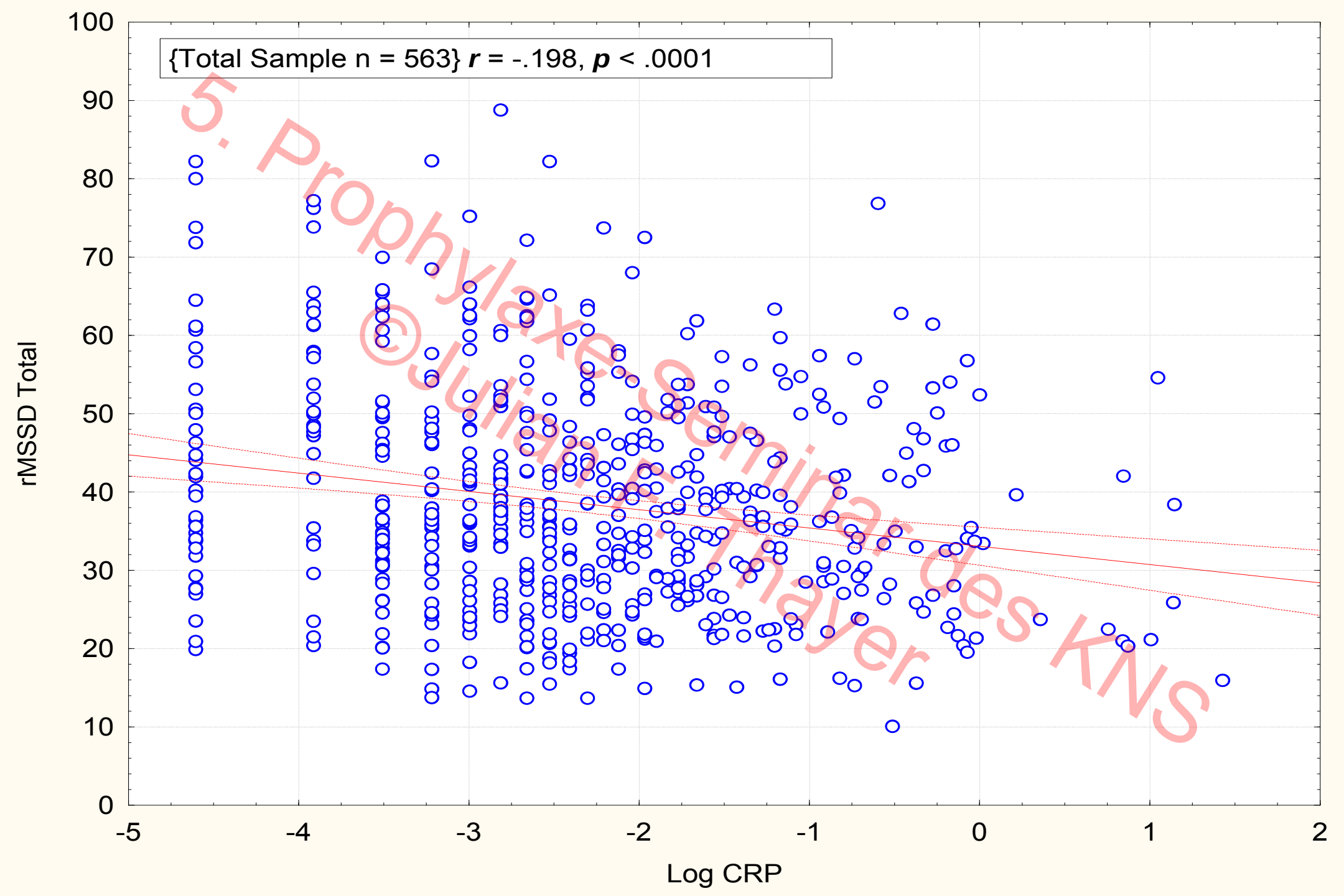
	All		Men		Women	
	Partial corr.	*P*-value	Partial corr.	*P*-value	Partial corr.	*P*-value
Gender	**−0.174**	**<0.001**	–		–	
Age	−0.028	0 0.51	0.050	0.25	**−0.474**	**<0.001**
Smoking status	**0.093**	**0.024**	0.066	0.13	0.143	0.31
History of hypertension	0.009	0.83	0.031	0.47	−0.098	0.48
History of myocardial infarction	0.060	0.14	0.050	0.25	n.a.	
Diabetes	0.026	0.52	0.028	0.53	0.023	0.87
Systolic blood pressure	**0.081**	**0.047**	**0.097**	**0.026**	0.003	0.98
Diastolic blood pressure	−0.025	0.54	−0.051	0.24	0.105	0.45
Body mass index	**0.293**	**<0.001**	**0.286**	**<0.001**	**0.283**	**0.04**
Haematocrit	**−0.091**	**0.026**	**−0.083**	**0.05**	−0.017	0.91
High-density lipoprotein	−0.005	0.91	−0.040	0.36	**0.30**	**0.027**
Low-density lipoprotein	0.044	0.28	0.048	0.27	0.167	0.23
Triglycerides	0.028	0.50	0.020	0.64	0.026	0.85
Habitual physical activity	−0.054	0.19	−0.064	0.14	−0.14	0.30
Urinary norepinephrine	−0.018	0.67	0.009	0.84	−0.156	0.27
RMSSD (ms)	**−0.119**	**0.003**	**−0.082**	**0.05**	**−0.359***	**0.008**

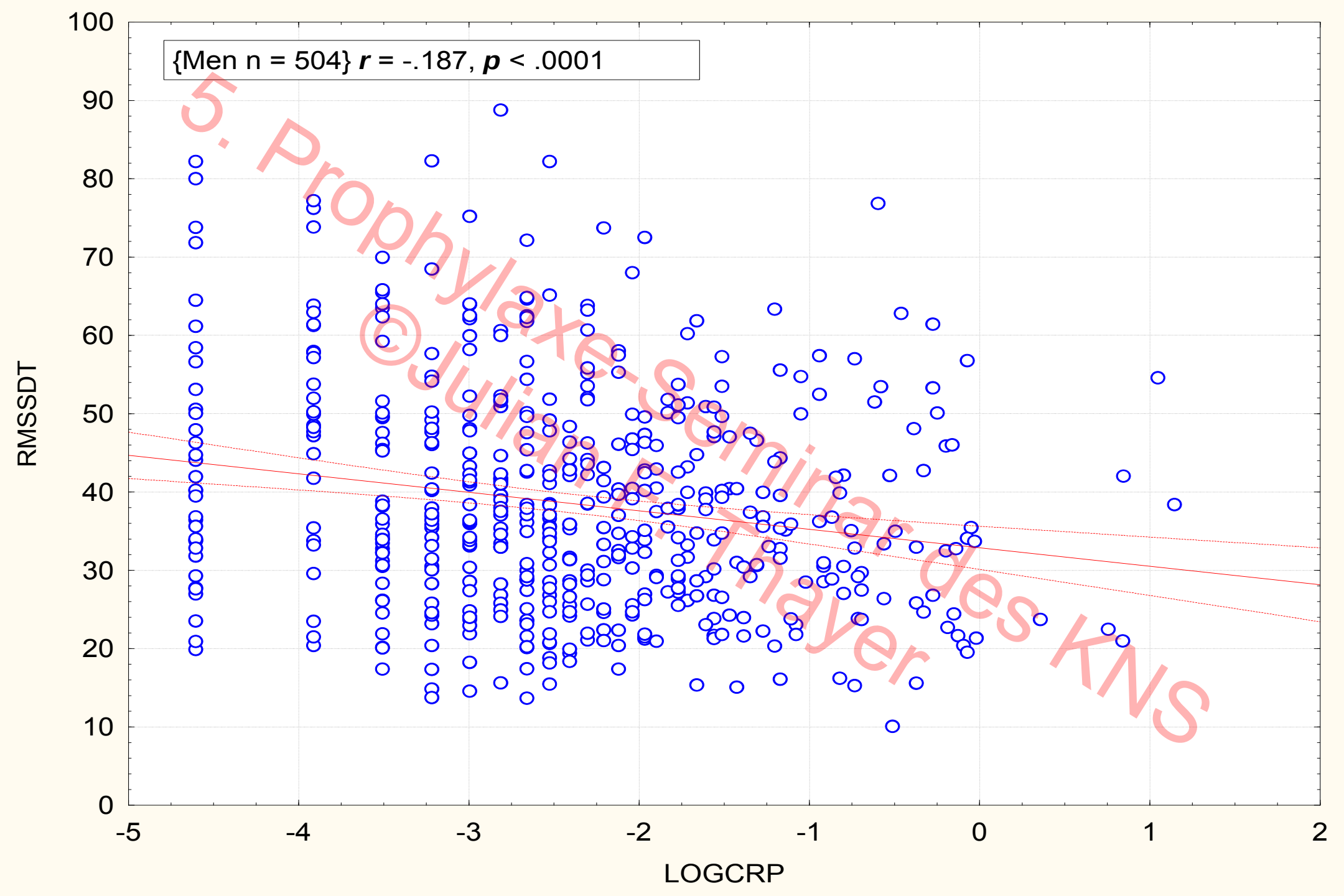
n.a, not applicable; Significant associations in **bold**; RMSSD, root mean square of successive differences; *significant partial r difference between males and females ($P < 0.05$); Model fit statistics: All [$F(16, 594) = 10.644$, $P < 0.0001$, $R^2 = 0.22$], Men [$F(15,529) = 9.61$, $P < 0.0001$, $R^2 = 0.21$], and Women [$F(14,51) = 3.12$, $P = 0.001$, $R^2 = 0.46$].

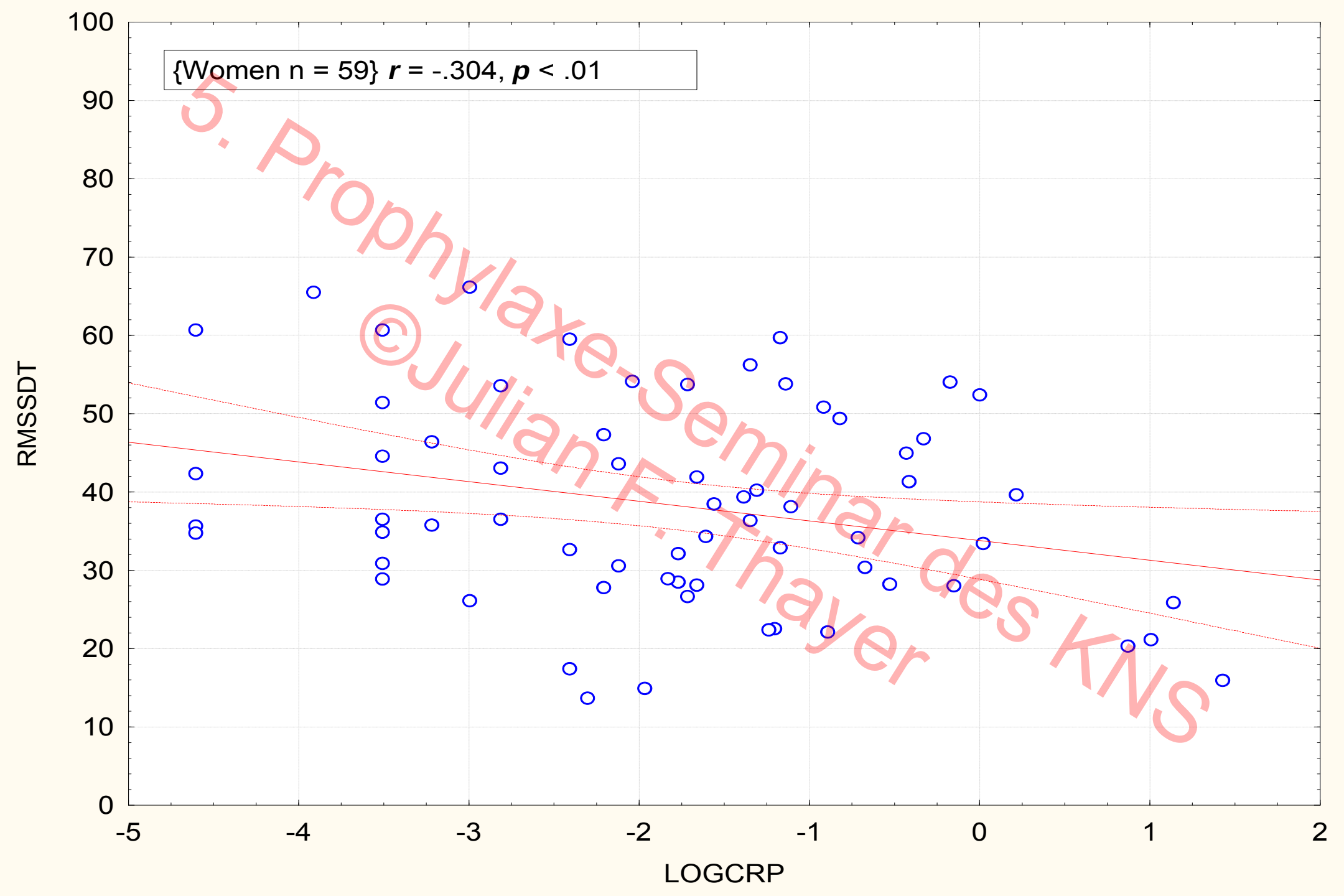
Table 4 Partial correlation coefficients with white blood cell count and RMSSD

	All		Men		Women	
	Partial corr.	*P*-value	Partial corr.	*P*-value	Partial corr.	*P*-value
Gender	−0.071	0.094	–		–	
Age	−0.041	0.314	−0.012	0.786	**−0.275**	**0.046**
Smoking status	**0.316**	**<0.001**	**0.324**	**<0.001**	0.128	0.361
History of hypertension	−0.017	0.674	−0.023	0.596	0.063	0.656
History of myocardial infarction	−0.005	0.901	−0.014	0.745	n.a.	
Diabetes	0.012	0.764	0.023	0.596	−0.080	0.567
Systolic blood pressure	**0.083**	**0.043**	**0.106**	**0.014**	−0.085	0.543
Diastolic blood pressure	−0.049	0.230	−0.063	0.149	0.052	0.712
Body-mass-index	**0.102**	**0.013**	**0.102**	**0.019**	0.095	0.499
Hematocrit	0.079	0.053	0.071	0.100	0.189	0.176
High-density lipoprotein	0.036	0.384	0.007	0.871	**0.271**	**0.050**
Low-density lipoprotein	−0.071	0.082	−0.068	0.116	−0.029	0.838
Triglycerides	**0.116**	**0.005**	**0.122**	**0.005**	0.049	0.728
Habitual physical activity	−0.064	0.120	−0.071	0.102	−0.062	0.661
Urinary norepinephrine	**0.103**	**0.012**	**0.109**	**0.012**	0.087	0.534
RMSSD (ms)	**−0.126**	**0.002**	**−0.101**	**0.020**	**−0.332**	**0.015**

n.a, not applicable; Significant associations in **bold**; RMSSD, root mean square of successive differences; Model fit statistics: All [$F(16, 594) = 10.22$, $P < 0.0001$, $R^2 = 0.22$], Men [$F(15,529) = 10.3$, $P < 0.0001$, $R^2 = 0.23$], and Women [$F(14,51) = 1.7$, $P = 0.084$, $R^2 = 0.32$].


{Total Sample n = 563} r = -.198, p < .0001
rMSSD Total
Log CRP
100
90
80
70
60
50
40
30
20
10
0
-5
-4
-3
-2
-1
0
1
2
5. Prophylaxe-Seminar des KNS
©Julian F. Thayer


{Men n = 504} r = -.187, p < .0001
RMSSDT
LOGCRP
100
90
80
70
60
50
40
30
20
10
0
-5
-4
-3
-2
-1
0
1
2
5. Prophylaxe-Seminar des KNS
©Julian F. Thayer


{Women n = 59} r = -.304, p < .01
RMSSDT
LOGCRP
100
90
80
70
60
50
40
30
20
10
0
-5
-4
-3
-2
-1
0
1
2
5. Prophylaxe-Seminar des KNS
©Julian F. Thayer

Summary

- Vagally mediated HRV is inversely related to CRP in men and women (pre-menopausal)
- Effect in men is comparable to effect of smoking
- Effect in women is comparable to effect of body mass index (4.4 times larger than males)
- Clinically relevant cholinergic anti-inflammatory effect

Rapid Communication
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Lower heart rate variability predicts increased level of C-reactive protein 4 years later in healthy, nonsmoking adults

M. N. Jarczok[1], J. Koenig[2], D. Mauss[3], J. E. Fischer[1,*] & J. F. Thayer[2,*]

Table 1 *Variables measured at baseline (2007) and at follow-up (2011) in all 106 participants*

	2007	2011
BMI, kg m^{-2}	24.55 (3.42)	25.34 (4.64)
SBP, mmHg	126.38 (13.25)	136.86 (13.26)
DBP, mmHg	80.47 (8.99)	80.53 (10.71)
CRP, mg L^{-1}	1.77 (1.81)	1.24 (1.34)
vmHRV, ms^2	235.86 (202.98)	–

All data are presented as mean (SD). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; vmHRV, vagally mediated heart rate variability.

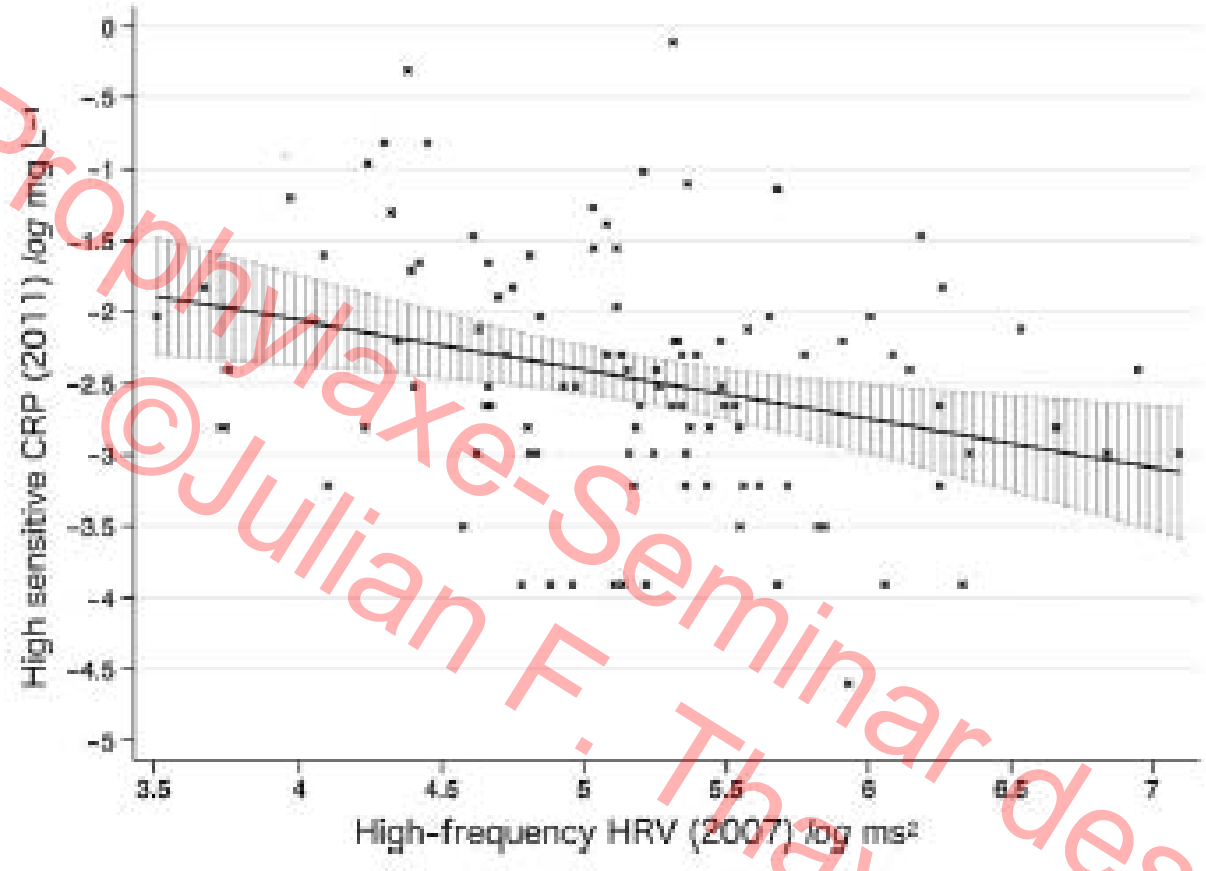

Fig. 1 *Scatterplot of high-frequency heart rate variability (HRV) at baseline in 2007 and high-sensitivity C-reactive protein (CRP) at follow-up in 2011. The regression line is shown (solid line) with the 95% confidence intervals (grey lines). Data are log-transformed.*

Heart Rate Variability is Associated with Glycemic Status After Controlling for Components of the Metabolic Syndrome ☆

Marc N. Jarczok [a,*], Jian Li [a], Daniel Mauss [a,b], Joachim E. Fischer [a], Julian F. Thayer [a,c]

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Table 2a
Pearson's Correlations between measures of fasting plasma glucose and HbA_{1C} with HRV.

	Glucose (mmol/l)	HbA_{1C} (%)
Participants (N)	3005	3003
HF (ms^2) ‡†	-0.271***	-0.214**
LF (ms^2) ‡†	-0.273***	-0.235**
RMSSD (ms) ‡†	-0.278***	-0.226**
SDNN (ms)‡	-0.222***	-0.171***
N/D HF (ms^2)†	-0.066***	-0.034
N/D LF (ms^2)†	-0.163***	-0.141***
N/D RMSSD (ms)†	-0.045*	-0.019
N/D SDNN (ms)	-0.094***	-0.097***

‡24 h average. †Log transformation for analysis. N/D = Night to Day- ratio.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

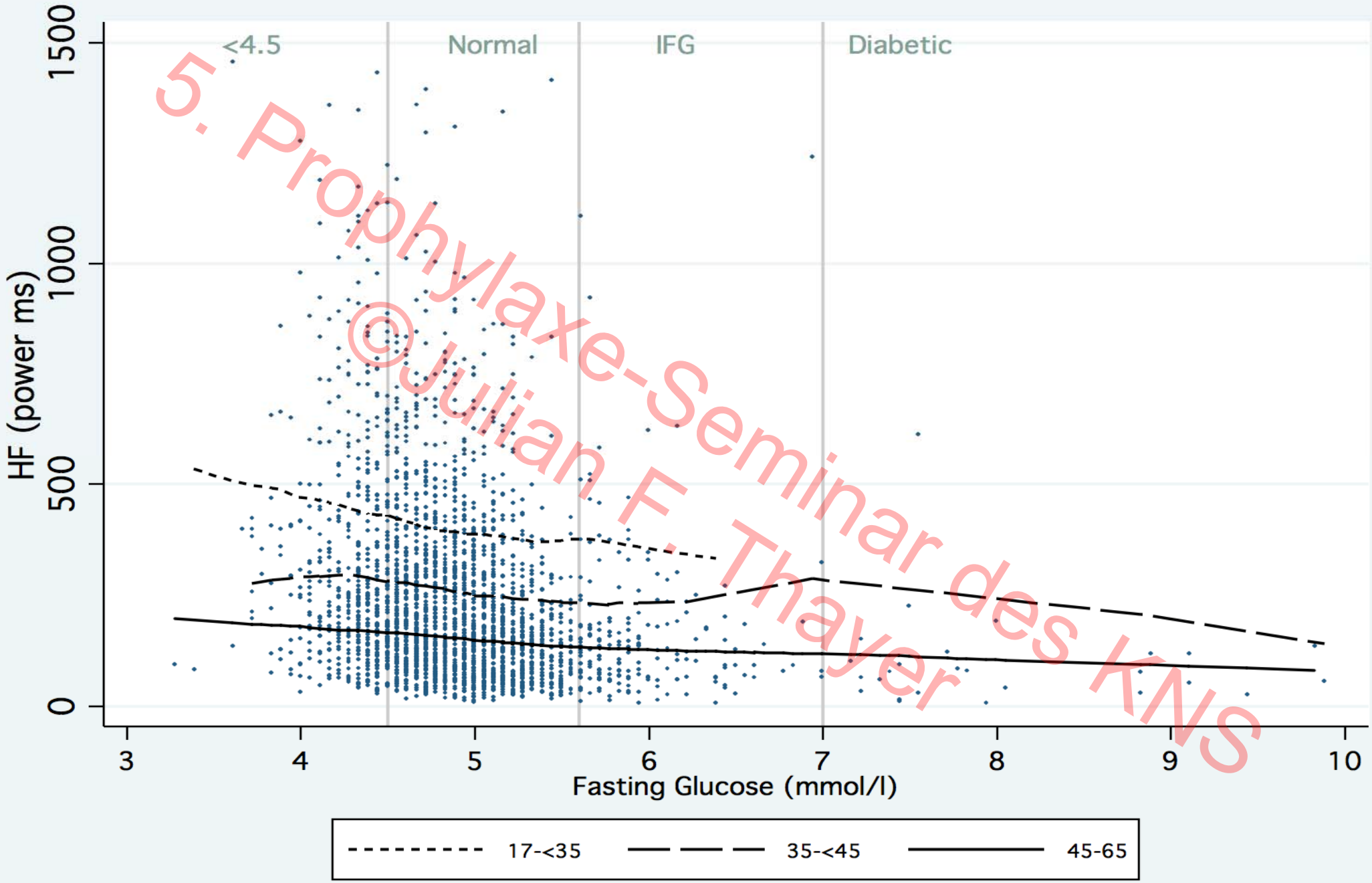
Table 2b
Pearson's Correlations between measures of MetS with HRV.

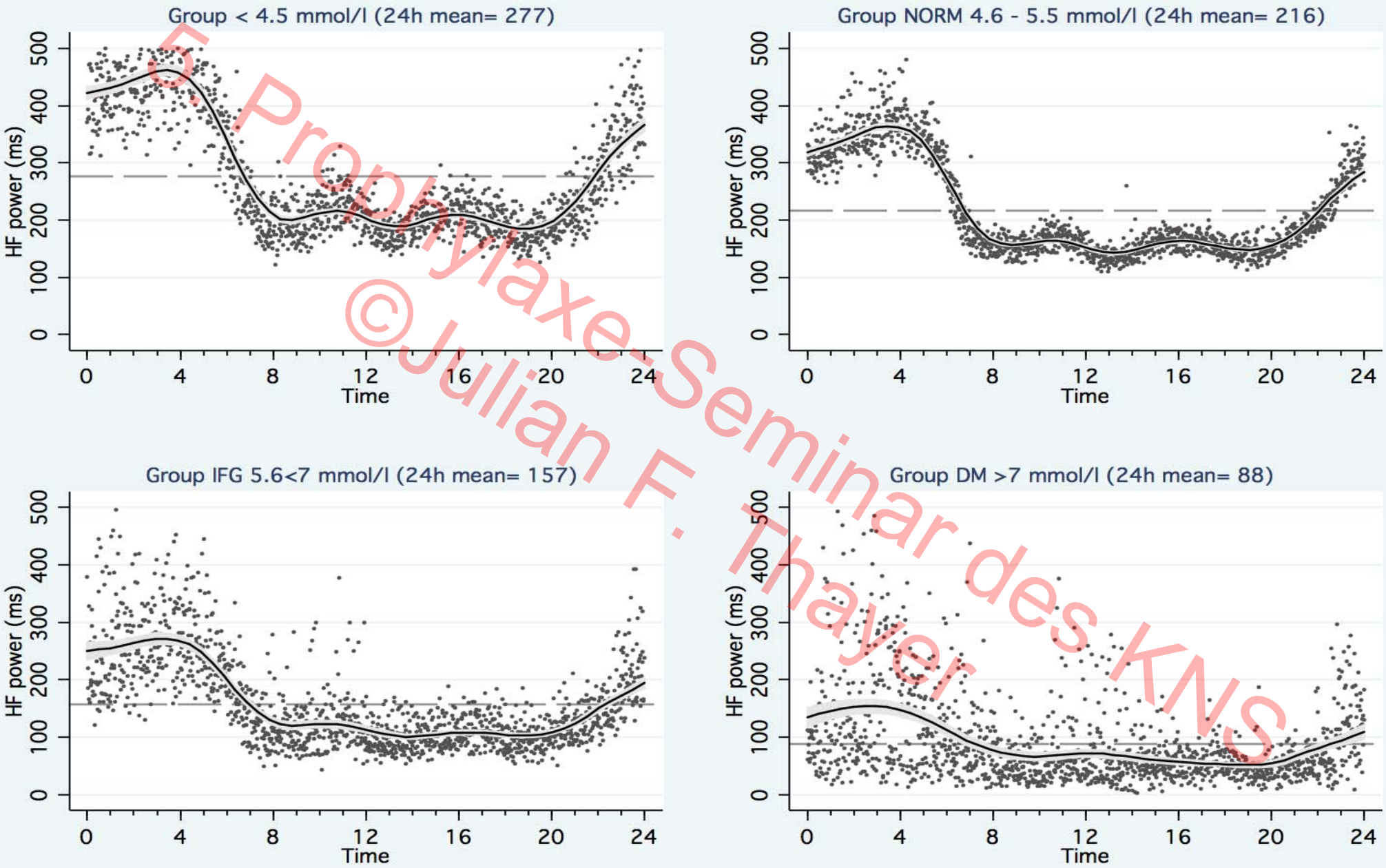
	Triglyceride	Waist Circumference	Systolic BP	Diastolic BP	High density lipoproteins
HF (ms^2) ‡†	-0.220***	-0.341***	-0.219***	-0.331***	0.079***
LF (ms^2) ‡†	-0.177***	-0.243***	-0.179***	-0.219***	-0.045*
RMSSD (ms)‡†	-0.222***	-0.332***	-0.203***	-0.327***	0.070***
SDNN (ms)‡	-0.183***	-0.211***	-0.121***	-0.220***	-0.004
N/D HF (ms^2)†	-0.022	-0.157***	-0.062**	-0.053**	0.107***
N/D LF (ms^2)†	-0.084***	-0.176***	-0.154***	-0.137***	0.054**
N/D RMSSD (ms)†	-0.020	-0.124***	-0.067***	-0.039	0.104***
N/D SDNN (ms)	-0.062***	-0.145***	-0.092***	-0.096***	0.112***

‡24 h average. †Log transformation for analysis. N/D = Day to Night to Day- ratio.
* $p<0.05$; ** $p<0.01$; *** $p<0.001$.

Table 3
Partial correlation coefficients with fasting plasma glucose.

	24 hour		Day		Night	
	Partial corr.	P-value	Partial corr.	P-value	Partial corr.	P-value
Age (years)	**0.095**	**<0.001**	**0.101**	**<0.001**	**0.082**	**<0.001**
Female (%)	-0.011	0.589	-0.013	0.524	-0.018	0.373
Current Smoker (%)	-0.004	0.860	-0.001	0.980	-0.013	0.514
Alcohol intake*	0.031	0.125	0.035	0.092	0.038	0.065
History of high lipids (%)	-0.024	0.244	-0.024	0.251	-0.030	0.143
History of high BP (%)	-0.006	0.765	-0.004	0.863	0.001	0.980
History of high glucose (%)	**0.330**	**<0.001**	**0.339**	**<0.001**	**0.339**	**<0.001**
History of CVD (%)	0.020	0.321	0.021	0.326	0.033	0.114
Hematocrit (%)	**-0.043**	**0.032**	**-0.052**	**0.014**	**-0.048**	**0.021**
C-reactive Protein (mg/dl)	0.012	0.555	-0.003	0.871	0.004	0.829
Waist Circumference (cm)	**0.137**	**<0.001**	**0.139**	**<0.001**	**0.124**	**<0.001**
High density lipoproteins (mg/dl)	-0.003	0.874	-0.003	0.882	-0.001	0.960
Triglycerides (mg/dl)	**0.087**	**<0.001**	**0.096**	**<0.001**	**0.089**	**<0.001**
Systolic BP (mmHg)	**0.058**	**0.005**	**0.045**	**0.032**	**0.052**	**0.011**
Diastolic BP (mmHg)	0.012	0.538	0.027	0.196	0.014	0.498
HF (ms^2)† ★	**-0.058**	**0.004**	-0.040	0.059	**-0.104**	**<0.001**
LF (ms^2)† ★	**-0.087**	**<0.001**	-0.041	0.053	**-0.106**	**<0.001**
RMSSD (ms)† ★	**-0.078**	**<0.001**	**-0.047**	**0.026**	**-0.114**	**<0.001**
SDNN (ms) ★	**-0.073**	**<0.001**	-0.037	0.079	**-0.087**	**<0.001**
Heart Rate (BPM)† ★	**0.056**	**0.006**	**0.041**	**0.048**	**0.078**	**<0.001**



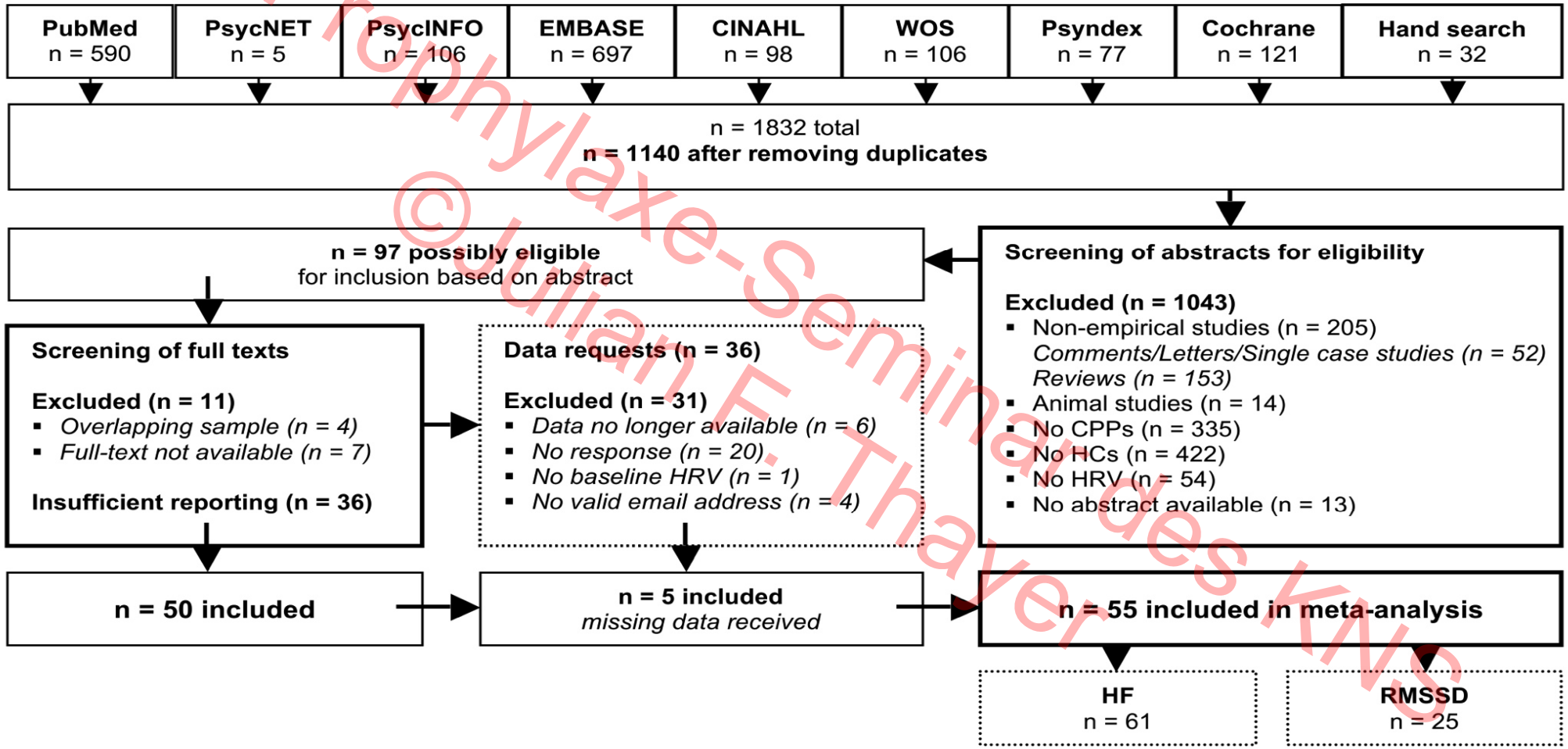


Conclusions

- HRV during sleep is related to gylcemic control as indexed by HbA1c and FG
- Diabetics and pre-diabetics have lower HRV than normal controls
- Implications for diabetic neuropathy

- Important in energy regulation

Vagal-activity in chronic pain patients compared to healthy controls

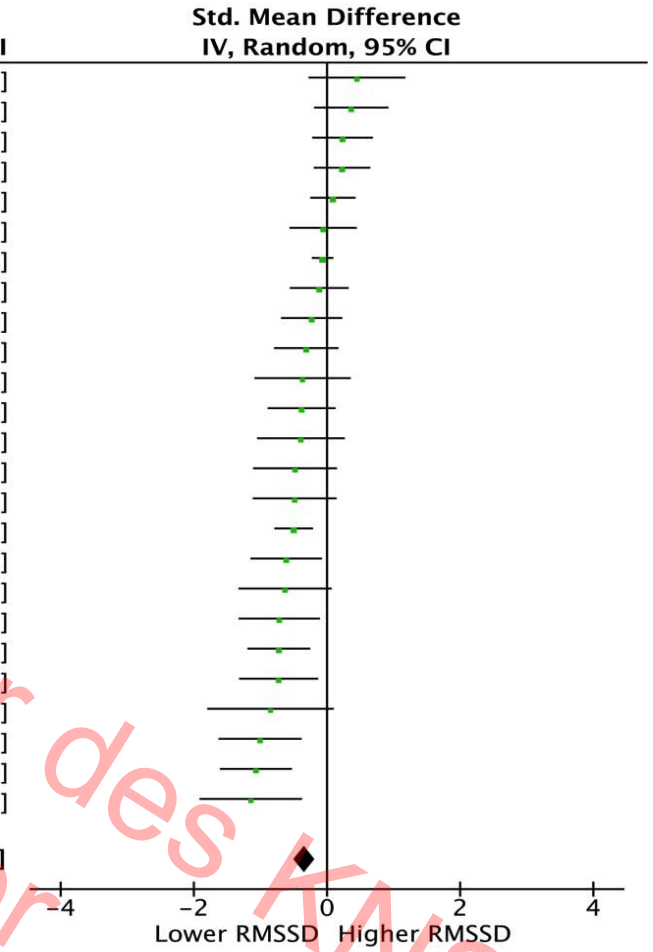


Koenig J, Falvay D, Clamor A, Wagner J, Jarczok MN, Ellis RJ, Weber CS, Thayer JF. Pneumogastric (Vagus) Nerve Activity indexed by Heart Rate Variability in Chronic Pain Patients compared to Healthy Controls - A Meta-Analysis. Under Review

Vagal-activity in chronic pain patients compared to healthy controls: main effect

Study or Subgroup	Chronic Pain Patients Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
40 – Nilsen et al.	85.2	42.8	16	68.9	23.8	14	2.9%	0.45 [−0.28, 1.18]
2a – Burr et al.	46.9	24.4	18	39	20	41	3.9%	0.36 [−0.19, 0.92]
2c – Burr et al.	43.6	18.9	34	39	20	41	4.6%	0.23 [−0.22, 0.69]
13 – Evrengül et al.	33.8	23.7	42	29.7	9.8	44	4.8%	0.23 [−0.20, 0.65]
22 – Heitkemper et al.	39.6	19.4	103	37.9	18.6	49	5.5%	0.09 [−0.25, 0.43]
35 – Martínez-Lavín et al.	42.53	17.73	30	43.5	15.64	30	4.2%	−0.06 [−0.56, 0.45]
33 – Maixner et al.	65.59	196.34	1494	77.99	24.74	166	6.8%	−0.07 [−0.23, 0.09]
2b – Burr et al.	36.9	14.9	38	39	20	41	4.7%	−0.12 [−0.56, 0.32]
25 – Jarrett et al.	3.56	0.47	35	3.69	0.63	38	4.5%	−0.23 [−0.69, 0.23]
48 – Stein et al.	37	14	29	43	22	39	4.4%	−0.31 [−0.80, 0.17]
6 – Chervin et al.	32	12	15	38	19	15	2.9%	−0.37 [−1.09, 0.36]
10 – De Kooning et al.	46.83	25.44	30	56.94	26.83	30	4.2%	−0.38 [−0.89, 0.13]
4c – Chelimsky et al.	39.05	27.25	12	50.91	30.48	36	3.3%	−0.39 [−1.05, 0.27]
17 – Gass & Glaros	46.2	38.14	21	63.79	33.19	19	3.4%	−0.48 [−1.11, 0.15]
50 – Terkelsen et al.	37	20	20	53	41	20	3.4%	−0.49 [−1.12, 0.14]
7 – Cho et al.	23	10.9	94	29	12.9	94	5.9%	−0.50 [−0.79, −0.21]
20 – Hallman et al.	41	17	29	56	30	27	4.0%	−0.61 [−1.15, −0.08]
45 – Singh et al.	44	42	20	76	59	14	3.0%	−0.63 [−1.33, 0.07]
31 – Lerma et al.	36	13.9	22	47.3	16.9	22	3.5%	−0.72 [−1.33, −0.11]
4a – Chelimsky et al.	31.97	20.74	38	50.91	30.48	36	4.5%	−0.72 [−1.19, −0.25]
2d – Burr et al.	25.9	9.7	16	39	20	41	3.6%	−0.73 [−1.32, −0.13]
14 – Figueroa et al.	2.9	0.8	10	3.5	0.5	9	2.0%	−0.85 [−1.80, 0.10]
37 – Mork et al.	23	11	23	37	16	22	3.4%	−1.01 [−1.63, −0.38]
4b – Chelimsky et al.	23.85	14.17	26	50.91	30.48	36	4.0%	−1.07 [−1.61, −0.53]
42 – Raj et al.	28.6	9.9	17	45.8	18.9	14	2.7%	−1.14 [−1.91, −0.37]
Total (95% CI)			**2232**			**938**	**100.0%**	**−0.34 [−0.50, −0.18]**

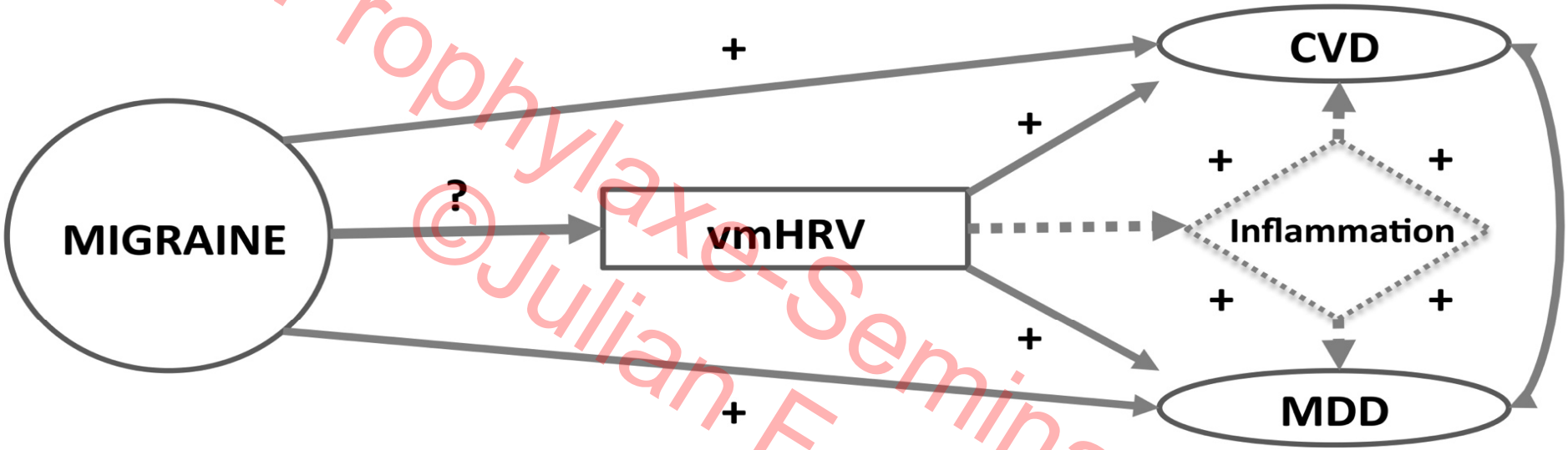
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 64.18$, df = 24 ($P < 0.0001$); $I^2 = 63\%$
Test for overall effect: Z = 4.14 ($P < 0.0001$)



Effect for HF (Z = 4.30, *p < .0001*; g = -0.29; 95% CI (-0.42, -0.16); k = 61) (Figure too large too illustrate on slide)

Koenig J, Falvay D, Clamor A, Wagner J, Jarczok MN, Ellis RJ, Weber CS, Thayer JF. Pneumogastric (Vagus) Nerve Activity indexed by Heart Rate Variability in Chronic Pain Patients compared to Healthy Controls - A Meta-Analysis. Under Review

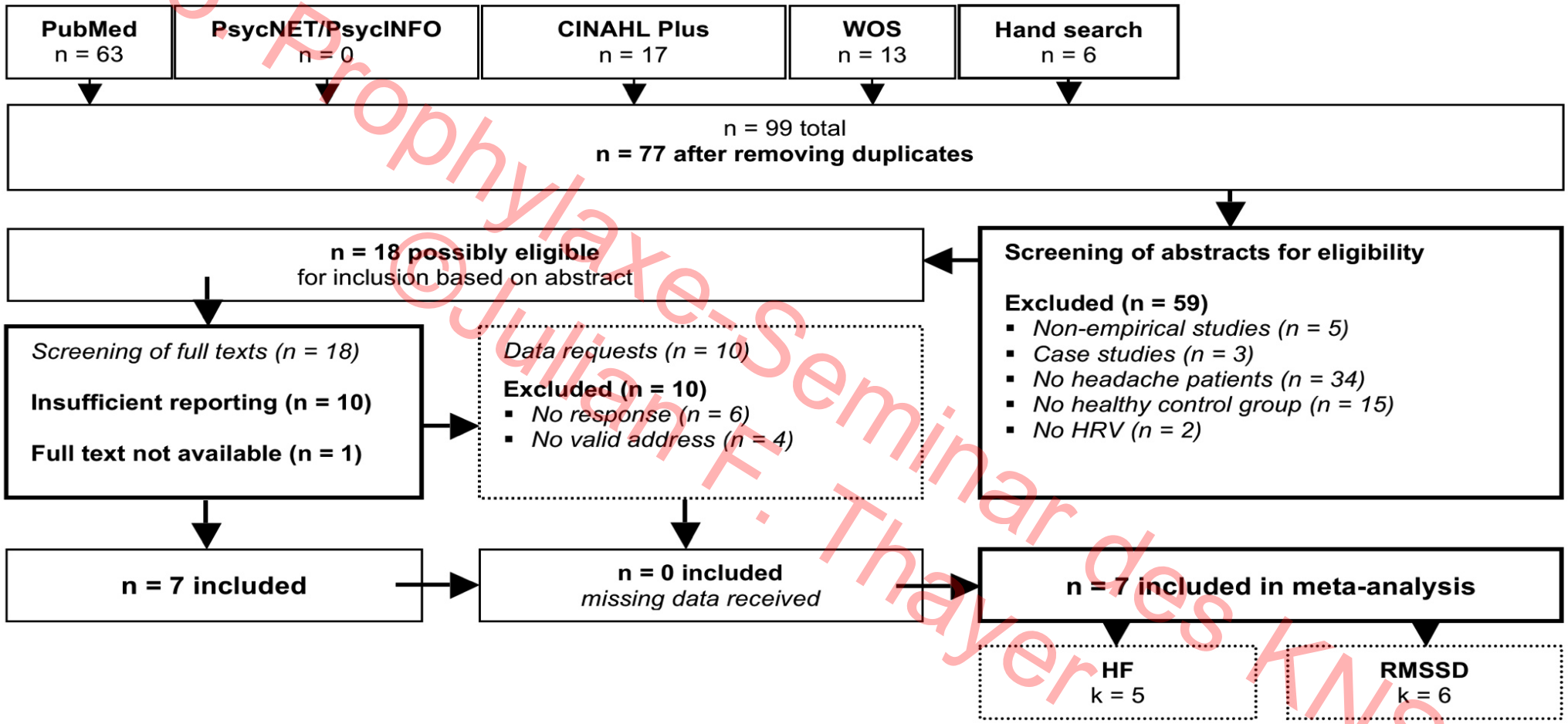
Vagal activity in patients with headache disorders compared to healthy controls



Established pathways in the association of Migraine, vmHRV, CVD, and MDD

Koenig J, Williams DP, Kemp A, Thayer JF. Vagally Mediated Heart Rate Variability in Headache Patients During Resting State – A Systematic Review and Meta-Analysis. Under Review

Vagal activity in patients with headache disorders compared to healthy controls

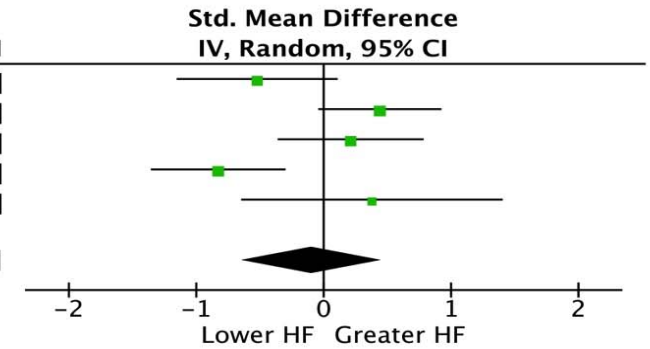


Koenig J, Williams DP, Kemp A, Thayer JF. Vagally Mediated Heart Rate Variability in Headache Patients During Resting State – A Systematic Review and Meta-Analysis. Under Review

Vagal activity in patients with headache disorders compared to healthy controls

Study or Subgroup	Headache Patients Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gass & Glaros 2013	49.5	19.44	21	63.79	33.19	19	20.2%	−0.52 [−1.15, 0.11]
Pierangeli et al. 1997 (a)	0.29	0.04	37	0.27	0.05	31	22.7%	0.44 [−0.04, 0.92]
Pierangeli et al. 1997 (b)	0.28	0.04	19	0.27	0.05	31	21.2%	0.21 [−0.36, 0.78]
Sanya et al. 2005	6.21	0.26	30	6.45	0.31	30	22.0%	−0.83 [−1.36, −0.30]
Tubani et al. 2003	9.043	3.796	8	7.654	3.002	7	13.9%	0.38 [−0.65, 1.41]
Total (95% CI)			**115**			**118**	**100.0%**	**−0.09 [−0.63, 0.45]**

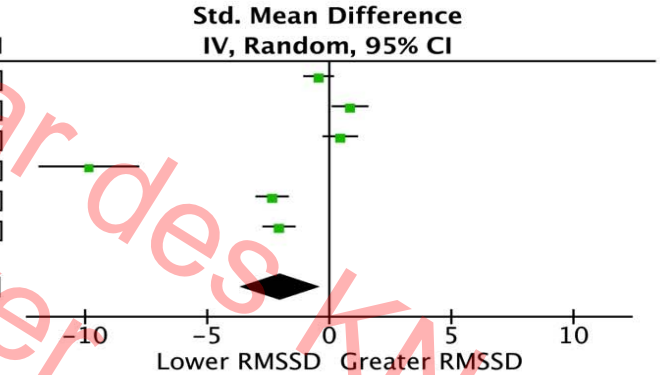
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 15.78$, df = 4 (P = 0.003); $I^2 = 75\%$
Test for overall effect: Z = 0.32 (P = 0.75)



HF-HRV (Z = 0.32, p = 0.75; g = -0.09; 95% CI [-0.63, 0.45]; k = 5)

Study or Subgroup	Headache Patients Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Gass & Glaros 2013	46.2	38.14	21	59.74	18.77	19	17.3%	−0.43 [−1.06, 0.19]
Nilsen et al. 2009 (a)	97.8	51.5	16	61.2	27.1	14	17.1%	0.85 [0.10, 1.60]
Nilsen et al. 2009 (b)	85.2	42.8	16	68.9	23.8	14	17.2%	0.45 [−0.28, 1.18]
Tabata et al. 2000	41.6	0.2	27	43.6	0.2	24	13.9%	−9.85 [−11.91, −7.78]
Thomsen et al. 1995 (a)	3.6	0.3	27	4.9	0.7	30	17.2%	−2.34 [−3.02, −1.65]
Thomsen et al. 1995 (b)	3.6	0.5	23	4.9	0.7	30	17.2%	−2.06 [−2.74, −1.38]
Total (95% CI)			**130**			**131**	**100.0%**	**−1.98 [−3.62, −0.33]**

Heterogeneity: $Tau^2 = 3.95$; $Chi^2 = 136.09$, df = 5 (P < 0.00001); $I^2 = 96\%$
Test for overall effect: Z = 2.36 (P = 0.02)



RMSSD (Z = 2.36, p = 0.02; g = -1.98; 95% CI [-3.62, -0.33]; k = 6)

Koenig J, Williams DP, Kemp A, Thayer JF. Vagally Mediated Heart Rate Variability in Headache Patients During Resting State – A Systematic Review and Meta-Analysis. Under Review

How to Modify HRV?

- Exericse
- Diet– Omega-3 Fatty Acids
- Stress reduction
- Pharmacological
- VNS

Fish Consumption and Heart Rate Variability

Preliminary Results

Anita L. Hansen[1,2], Lisbeth Dahl[3], Lene Bakke[4], Livar Frøyland[3], and Julian F. Thayer[5,6]

Journal of Psychophysiology 2010; Vol. 24(1):41–47

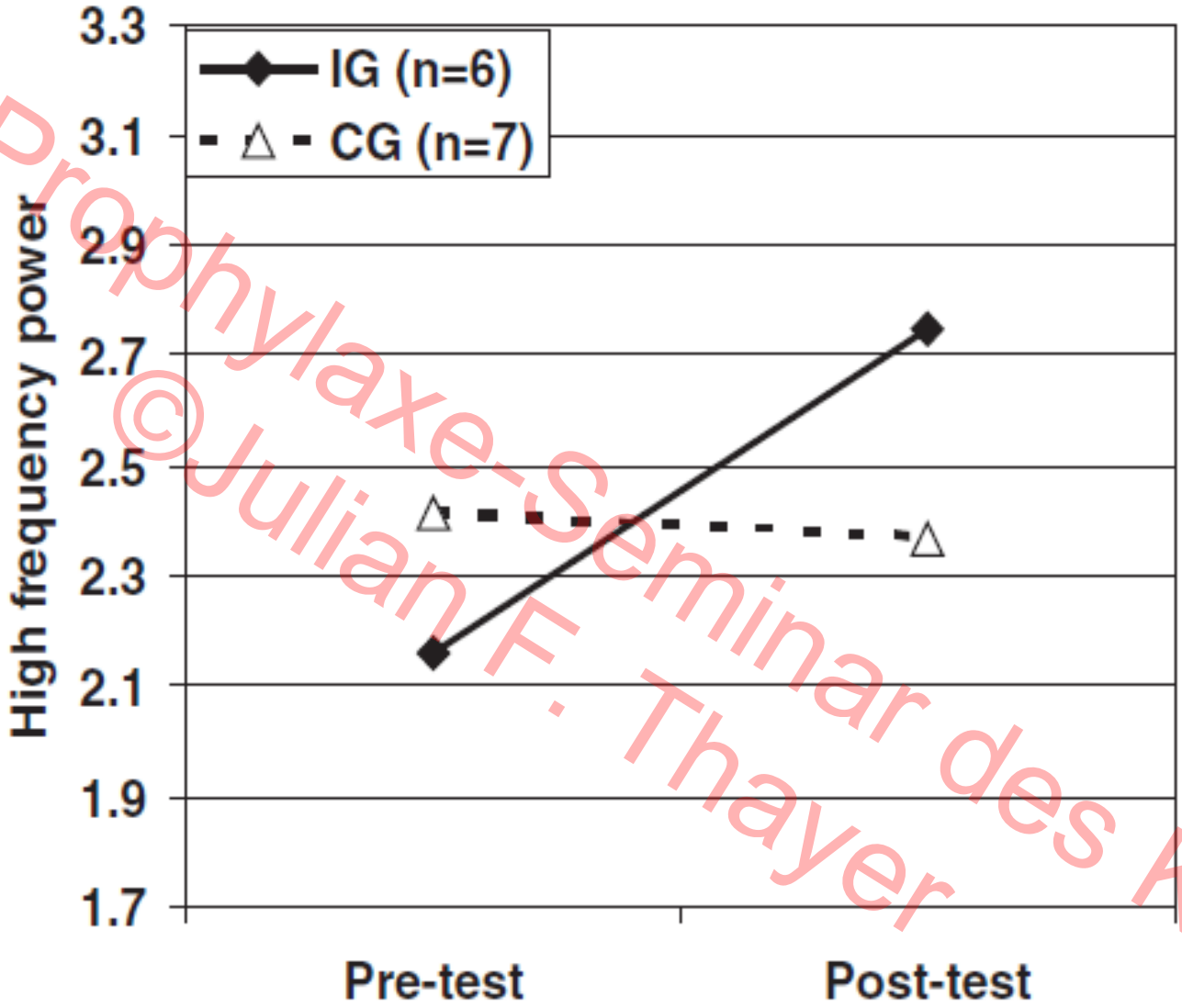


Figure 2. High-frequency (HF) power during pre- and post-test in intervention (IG) and control (CG) groups.

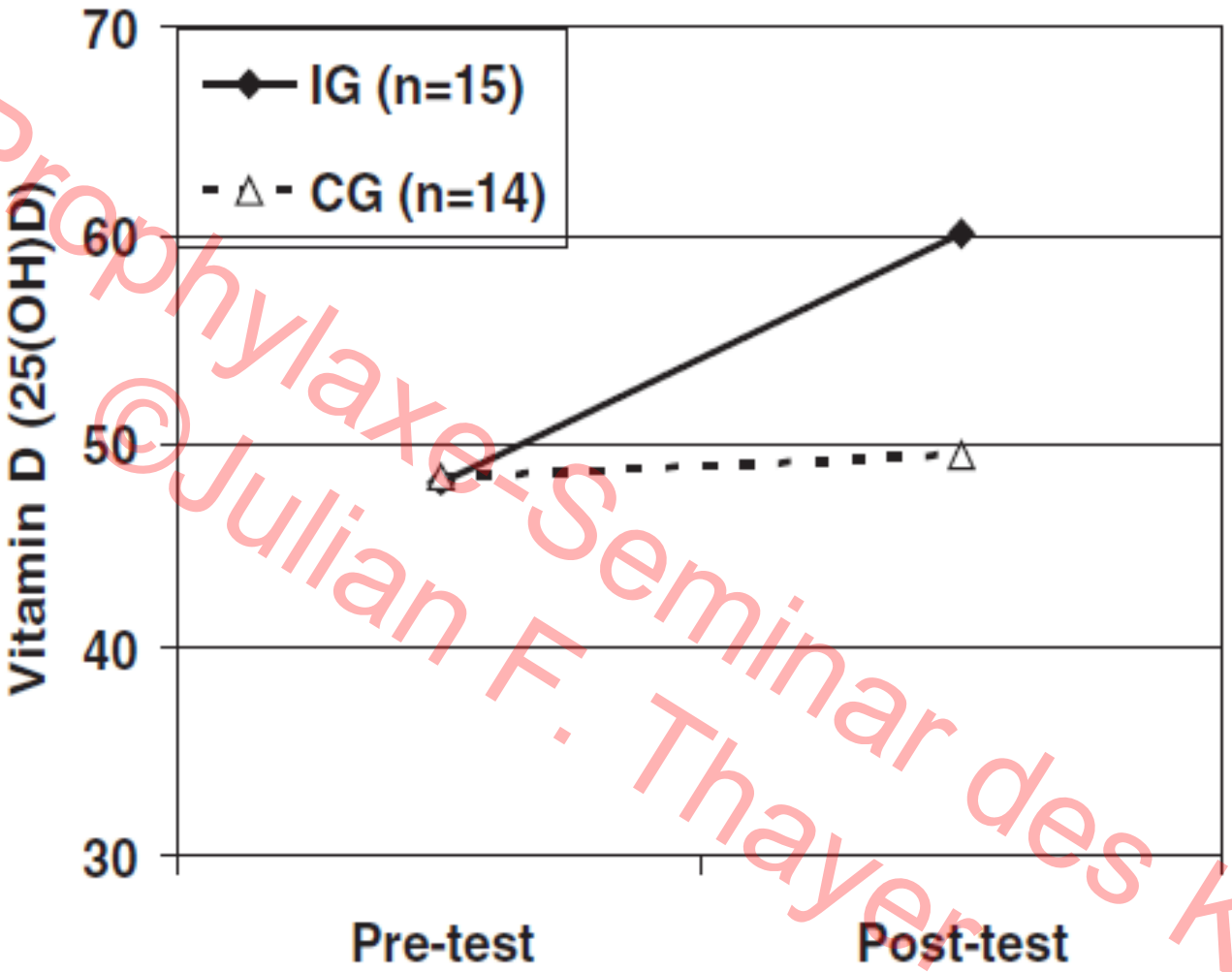


Figure 1. Vitamin D levels measured as 25(OH)D (nmol/L) during pre- and posttest in intervention (IG) and control (CG) groups.

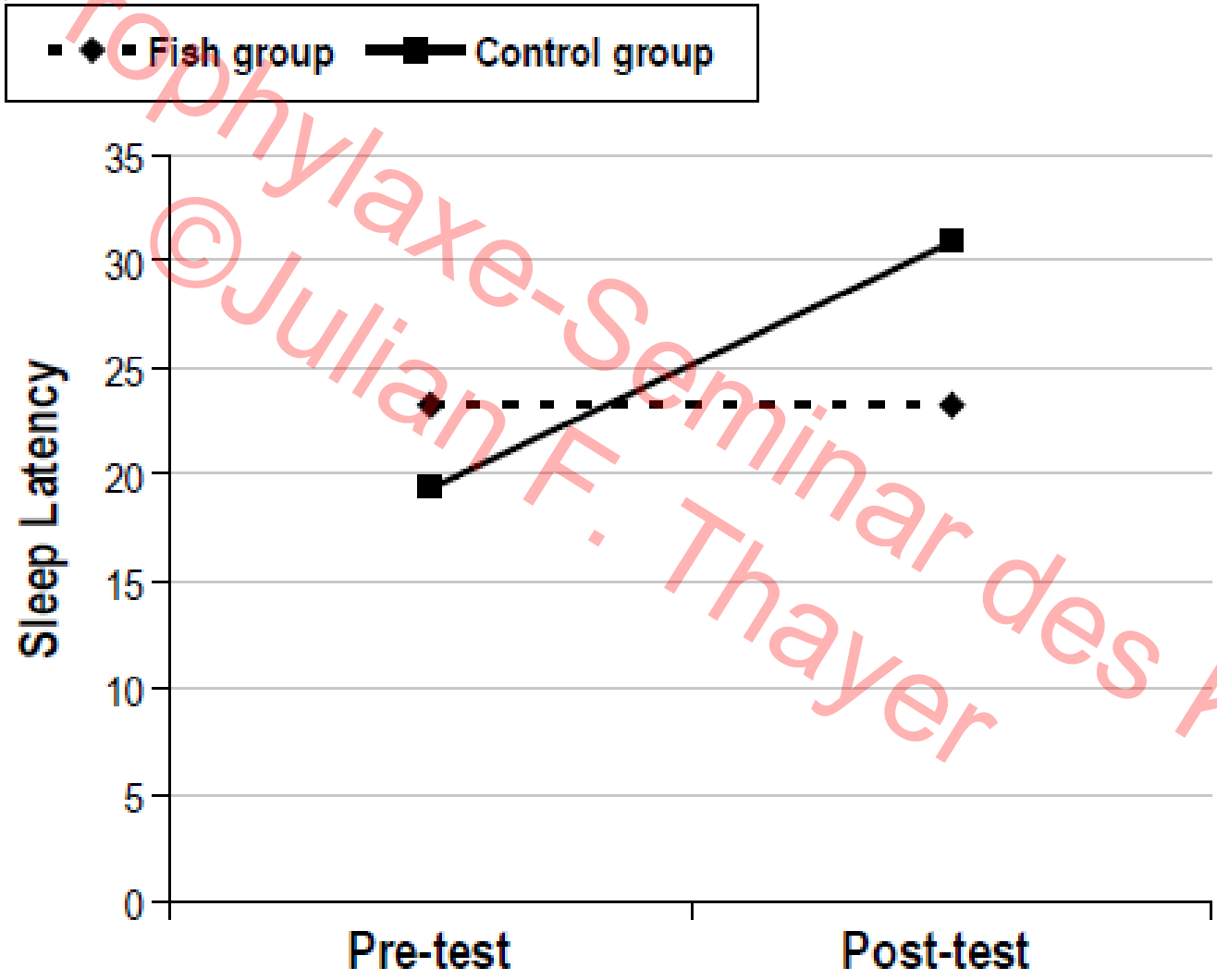
Fish Consumption, Sleep, Daily Functioning, and Heart Rate Variability

Anita L. Hansen, Ph.D.[1,2]; Lisbeth Dahl, Ph.D.[3]; Gina Olson, B.S.[4]; David Thornton, Ph.D.[4]; Ingvild E. Graff, Ph.D.[3]; Livar Frøyland, Ph.D.[3]; Julian F. Thayer, Ph.D.[5,6]; Staale Pallesen, Ph.D.[1,7]

Journal of Clinical Sleep Medicine

http://dx.doi.org/10.5664/jcsm.3714

Figure 2—Sleep latency (minutes) for both groups from pre- to post-test.

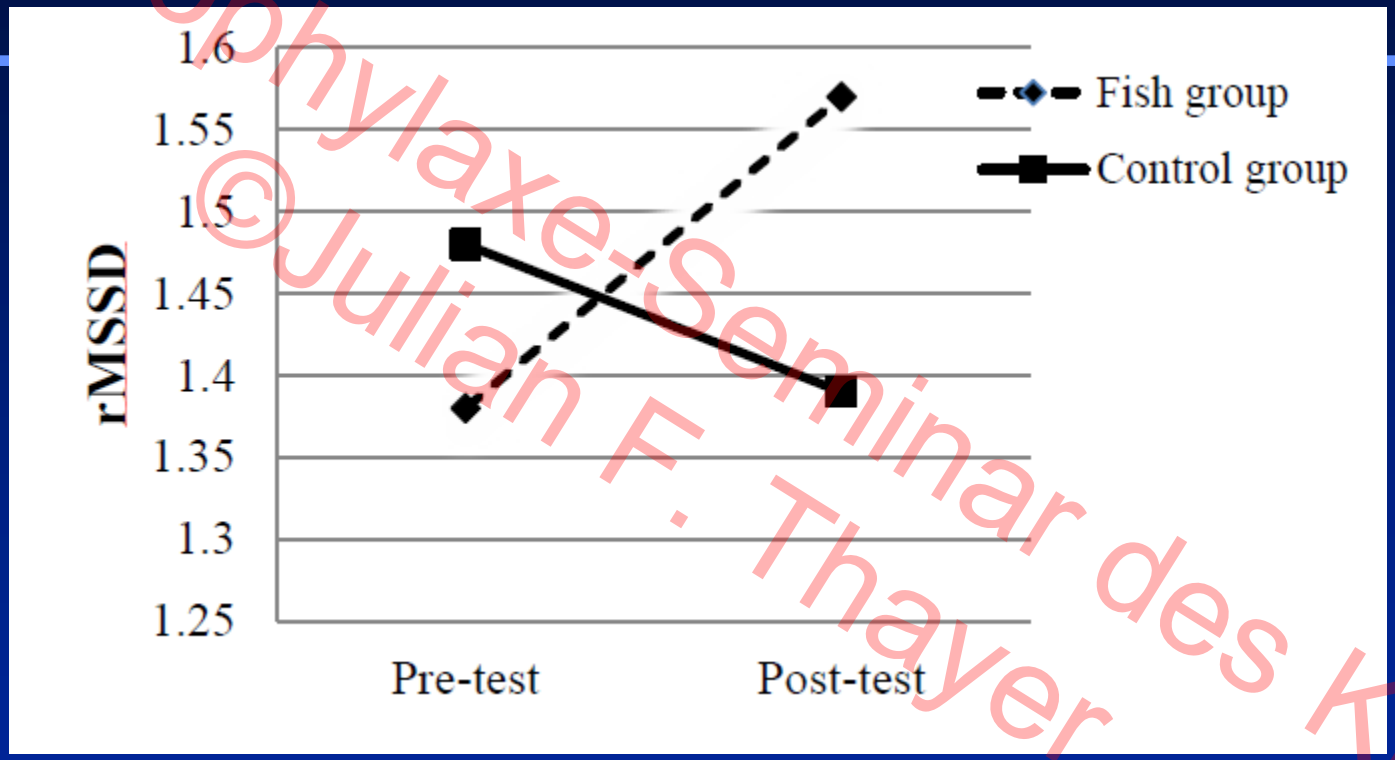


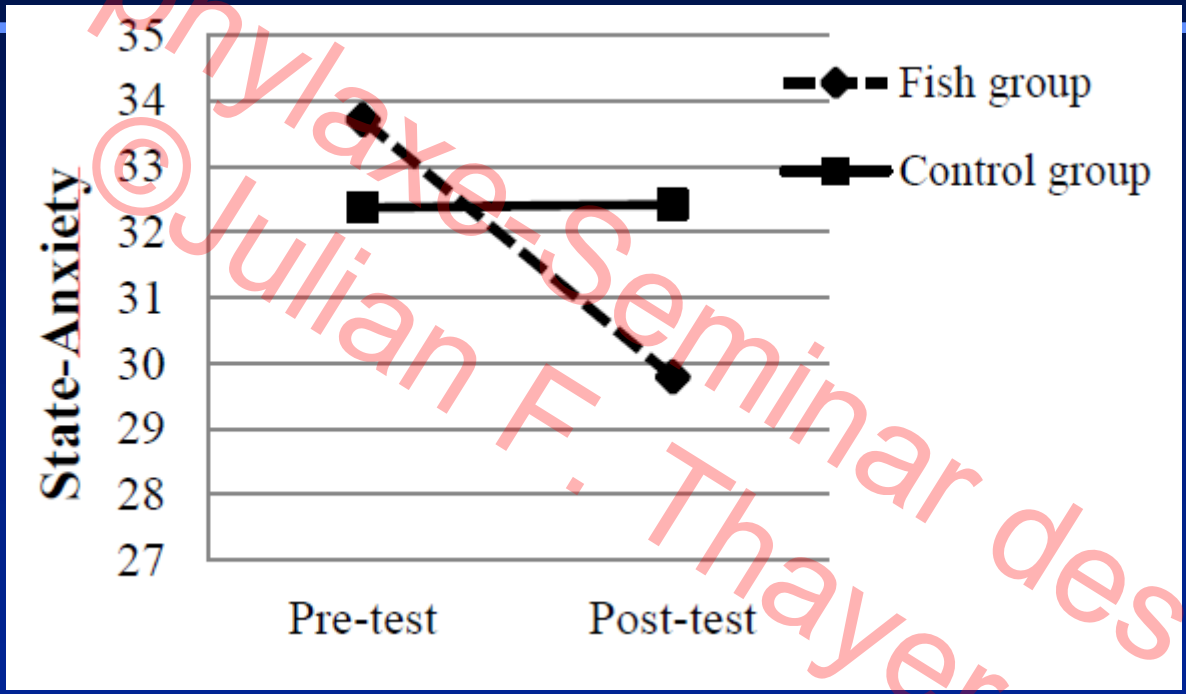
	Control Group		Fish Group	
	Pre	Post	Pre	Post
Psychophysiology				
HF-baseline	2.33 (0.57)	2.45 (0.58)	2.15 (0.58)	2.21 (0.60)[a,*]
N	23	23	34	34
HF-recovery	2.55 (0.46)	2.34 (0.49)	2.59 (0.78)	2.61 (0.62)
N	18	18	31	31

Reduced Anxiety in Forensic Inpatients after a Long-Term Intervention with Atlantic Salmon

Anita L. Hansen [1,2,*], Gina Olson [3], Lisbeth Dahl [4], David Thornton [3], Bjørn Grung [5], Ingvild E. Graff [4], Livar Frøyland [4] and Julian F. Thayer [6]

Nutrients **2014**, *6*, 5405-5418; doi:10.3390/nu6125405





“According to Darwin’s *Origin of Species*, it is not the most intellectual of the species that survives; it is not the strongest that survives; but the species that survives is the one that is best able to adapt and adjust to the changing environment in which it finds itself.”
Megginson (p. 4, 1963)

THANK YOU!